Eco-evolutionary modelling of infectious disease and host resistance

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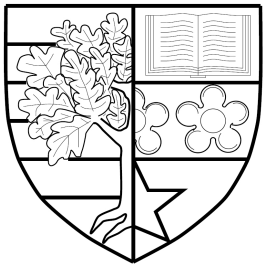

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Abstract

In this work we take an evolutionary invasion analysis approach to modelling evolution and use it to describe the selection pressures underlying epidemiological traits in natural host populations harboring endemic infections. Throughout this work a logistic form for host-birth rate allows for disease dependent population dynamics so that the detrimental effects of infection can be modelled and we also consider the more neglected detrimental effect whereby infection is linked to infertility. To begin with we give a theoretical introduction to the framework of adaptive dynamics and illustrate it through the established example of the evolution of parasite virulence. We then extend the results to account for condition dependent virulence which is an interaction between host condition (i.e. host stress) and virulence, that has recently generated much attention from empiricists. Many natural systems are seasonal, potentially leading to seasonal stress, and we show how to conduct a study for seasonal host populations and analyse its role in the evolution of density dependent virulence. We then turn our attention to the evolution of resistance beginning with a perspective on the relationship between investment in acquired immunity and the lifespan of hosts and parasites. In our penultimate chapter we derive explicit expressions for optimal investment in the various modes of resistance for a range of epidemiological scenarios. These expressions are then key to understanding our final chapter where we elaborate further on the established theory by allowing for parasite diversity. The final chapter highlights the central role played by specificity in the evolution of host defence. Since our approach throughout has been to build complexity onto a baseline model we conclude our discussion with a short section interpreting established results on the coevolution of virulence and resistance from the perspective of our results on the evolution of virulence and resistance.

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Chapter 1

Introduction

Infectious diseases place an enormous burden on medical and veterinary systems and therefore have a major economic impact on agriculture, conservation, and healthcare [1]. Parasites and their hosts are subject to evolution and this make disease management challenging [2]. In addition, complex feedbacks occur between the evolutionary process and the underlying population dynamics (eco-evolutionary feedbacks) which not only shape the evolutionary outcome but also determine the dynamic state of the host population [3]. Therefore for practical and for economic reasons connected to quality of life, but also to further our understanding of the natural world it is important to study the ecology and evolution of infectious disease. In this work we analyse the evolution of infectious disease and host resistance taking account of the ecological interaction of the host and parasite.

The abundances of host and parasite populations are dynamic variables that may change over time as a result of interactions between individuals within the host or parasite population (i.e. intra-specific interactions), interactions with individuals from other populations (i.e. inter-specific interactions), as well as interactions with biotic and abiotic environmental resources. It is increasingly recognised that the ecology of a population is a key determinant of selection pressures [4] and therefore of evolution through natural selection (as well as evolution through random drift and mutation both of which depend on population size [5]). The ecology and evolution of infectious disease systems can be studied in a number of ways across a number of scales ranging from molecular studies *in vitro* to empirical field studies, as well as to mathematical and computational modelling. Mathematical modelling has proved useful in a number of ways, for example, quantitative models can be closely coupled with experimental studies [6] and computational models such as agent based simulation can explore complex scenarios [7]. However, in ecology and evolution it is arguably the simple conceptual models, which focus on qualitative and not quantitative patterns, that have been most valuable in exploring, developing and occasionally disproving biological intuition [8]. For example, simple models have

shown that lethal parasites need not be maladapted to their hosts as had previously been assumed [2] and that evolution can favour phenotypes that create a difficult environment for new mutants to invade as opposed to optimising overall population level fitness (for example, natural selection favours resource consumers with the highest tolerance for low resource conditions in models of competition between consumers in [9]). In this work we use a theoretical modelling approach to shed light on key problems in the ecology and evolution of infectious disease.

1.1 Ecological and epidemiological modelling

Broadly, there are two scales from which to view infection dynamics, the between host scale and the within host scale. Although molecular aspects of disease transmission and pathology are key to understanding pathogenesis their precise detail is relatively unimportant in the dynamics at the population level (where a functional description often suffices). The most successful models of disease transmission have focused on interacting subpopulations of the host based on infection status [2]. The idea is that a key determinant of disease spread is the transmission bottleneck, i.e. the supply of fresh susceptible hosts for new infections, and this is strongly influenced by the frequency of uninfectable hosts (i.e. individuals who are immune to infection). The models of Anderson and May [2] which are themselves developments of earlier models of Kermack and McKendrick [10] and Ross [11] partition the host population into subpopulations of susceptibles, infecteds and immunes/recovereds (i.e. SIR models). When the infectious agent is a microparasite (i.e. fast generation time, small size and within host reproduction) it is not usually necessary to explicitly model parasite numbers [12]. The SIR paradigm has been very successful in modelling microparasites and many examples of disease intervention and control are based on results from such models (see, for example, the review of Hollingsworth [13]). In models of infectious disease in humans it is often assumed that the host population is at equilibrium so that the spread of infection alters only the frequencies of the epidemiological states (this requires that the disease does not alter the overall population density). However, for infectious diseases of wildlife the infection may well alter the density of hosts because of disease induced mortality, leading to disease dependent population dynamics. Therefore an important extension to the basic SIR models of Kermack and McKendrick [10] for disease dependent populations, that we use throughout this work, is the inclusion of vital dynamics, i.e. a more realistic birth or immigration process. In particular, the birth rate in naturally occurring populations may be dependent on host density and it is often assumed that the birth rate decreases with increasing host density so that the overall host density never exceeds an environmental carrying capacity (i.e. host population growth is

often modelled by a logistic growth curve [14]). This results in important feedbacks between the frequencies of the epidemiological states, the disease dependent population dynamics and the density dependent birth rate of new susceptibles, and these factors are all key in the spread of infection. Additional important extensions to the SIR framework include: the addition of an exposed class based on a latency period during which a host is infected but not infectious [2], the inclusion of maternal immunity (i.e. when newborns are not fully susceptible [15]), non-constant contact rates [16], the incorporation of heterogeneity in a variety of factors such as age and space [17], and a community representation of parasites [18–20]. However, an enduring consideration in models of this nature is the balance between simplicity and complexity so that many of these extensions are often omitted from simple models.

Since the beginning of the last century a number of important advances have been made in the modelling of infectious disease. For example, a key measure is R_0, the basic reproduction number or expected lifetime production of the disease [10]. If $R_0 > 1$ then, on average, a newly introduced infection will grow in a virgin host environment. R_0 is key to distinguishing between infections that are a viable threat and those that are not [21]. When $R_0 > 1$ and the disease spreads in a population it may exhaust itself and the parasite may become extinct because of a decrease in the supply of susceptibles (as will occur if the addition of new susceptibles to the host population is insufficient). Infection dynamics of this type are termed epidemic and if the overall host population is assumed to be density independent and there is long-lasting immunity this outcome is likely. In contrast to epidemic dynamics, the prevalence of infection may instead tend towards a non-zero endemic steady-state where, on average, every infected individual replaces itself exactly once [17] (endemic disease is likely if the production of new susceptibles is sufficiently large). Furthermore, transmission itself may be seasonal so that endemic population levels follow a periodic equilibrium if transmission varies smoothly across seasons. Alternatively, the epidemic boom and bust cycle may repeat itself periodically because of seasonal transmission in epidemic models, but this occurs with significant temporal spacing between epidemics unless there is a high rate of waning immunity. Endemic SIR models do not usually produce limit cycle behaviour but do approach their endemic equilibrium state through damped oscillations. The combination of damped oscillations with seasonal parameters such as contact rate or host reproduction rate can lead to periodic, quasi-periodic or chaotic population dynamics through nonlinear dynamic resonance [22] (i.e. two or more aspects of the system's dynamics are periodic and are mutually amplifying when in phase). Furthermore, host-microparasite systems with discrete, non-overlapping generations can lead to chaotic dynamics [23]. The quasi-periodic nature of time-series for several disease systems has been explained with great effect by reference to non-linear resonance of damped oscilla-

tions and periodic transmission rates (as, for example, with childhood measles and rubella in Altizer et al [22]).

1.2 Evolutionary modelling

Evolution can be defined as change in the genetic composition of a population over time. When phenotypic variation is heritable natural selection can lead to adaptation of the evolving population. Key to predicting and understanding evolution is the notion of fitness. Many mathematical descriptions of fitness have been proposed [24] and in general there are many ways to model evolution [25]. The modern synthesis has focused on Mendelian inheritance and its impact on the genetic composition of populations through generations with many key results (for example, Hardy-Weinberg proportions between allele and genotype frequencies in randomly mating populations [5]). With genetic detail (i.e. modelling alleles at specific loci) comes a level of complexity and for simplicity fitness in population genetics is often taken as a constant value of viability. Since constant fitness ignores the dynamic relationship between organisms and their biotic and abiotic environment the focus on genetics has often been at the expense of ecology which is of fundamental importance in determining selection pressures in natural populations. Quantitative genetics analyses the impact of evolution on phenotypic distributions over quantitative characters (i.e. many genes contributing to a phenotype in contrast to population genetics) and so focuses on the factors that determine phenotypic variance in populations (e.g. relatedness, heritability and epistasis [26]). Life-history evolution is generally based on quantitative traits because naturally occurring phenotypes are more often determined by the combined action of alleles at many loci and because so little is known of the genotype to phenotype mapping. Models of life-history evolution have often avoided ecological feedbacks (e.g. by using density independent Leslie matrices [27] or by optimising simple fitness measures).

In studies of pathogen evolution it is common to maximise the expected number of infections produced by a single infected host individual in an otherwise uninfected host population (i.e. maximisation of R_0). However, a mutant parasite's fortunes will more generally depend on the preceding phenotype's depletion of the host environment and density dependence in epidemiological terms can make this important (see, for example, Pugliese [28] which incorporates density dependence in host mortality). Other frameworks have combined demography and quantitative genetics [29, 30] with great success though a fixed phenotypic variance is usually assumed. Additional considerations include frequency dependent fitness, where the success of a strategy depends on the strategies of others with whom organisms are in competition [4].

The modern framework of evolutionary invasion analysis, which is often assessed under the framework of adaptive dynamics, asks what happens to the stability of an ecological system consisting of organisms with a resident trait when it is invaded by a low density of individuals with a mutant phenotype [31, 32]. Fitness is formulated in terms of invasion fitness which is equivalent to the intrinsic rate of growth of the mutant population. Lande [29] showed that the intrinsic population growth rate is the appropriate measure of fitness that is maximised (under certain assumptions, see Lande [29]). Since fitness is explicitly derived from a density dependent ecological model evolutionary invasion analysis can encompass density and frequency dependent evolution. Moreover, evolutionary invasion analysis combines the game theoretic concept of unbeatable strategies with the notion of convergence stability ensuring that evolutionary end points can actually be reached by an evolving population. Genetically it assumes polygenic quantitative characters (since phenotypes are assumed to be continuous) with very small variance since diversity arises only through rare mutations of small effect. It additionally requires weak selection because mutations are assumed to be rare and of small effect so that there is a separation of ecological and evolutionary time scales. Therefore evolutionary invasion analysis is broad in terms of its capacity to incorporate ecological phenomena such as density and frequency dependence, but is restrictive in terms of its genetic and mutational assumptions (however, these assumptions can be relaxed in stochastic simulations).

Modelling approaches based on population genetics focus on the role of genetic structure and its interplay with stochasticity. They have produced classical results such as equilibrium heterozygosity under the forces of mutation and drift in single locus models [26] and genetic hitch-hiking in multi locus models [33] (i.e. the fixation of neutral or even deleterious alleles due to their genetic proximity to loci with advantageous alleles). The approach of life-history evolution in contrast is centred on ecology and describes the ways that ecology feeds back to evolution to produce phenotypes. Examples of classical results in life-history evolution include the explanation of optimal reproductive strategies as adaptations to environmental conditions [34]. Populations which find themselves frequently far from equilibrium may often be r-selected (i.e. selected to reproduce fast and die young), while more stable populations may often be be k-selected (i.e. selected to increase their carrying capacity [35]). The contrasting phenomena of r and k selection have been used to explain the semelparity of some populations (i.e. reproductive strategies with only one reproduction event followed by death [36]) and the iteroparity of others (i.e. reproductive strategies with multiple reproduction events [36]). These key results in life-history evolution can be demonstrated in relatively simple optimisation models. The more recent framework of evolutionary invasion analysis allows for complex

ecological feedbacks, and it is now well established that this can lead to the phenomenon of evolutionary branching which may be a basis for sympatric speciation (i.e. adaptive speciation as opposed to allopatric speciation which is instead due to geographical separation of lineages, however adaptive speciation is problematic in sexually reproducing populations, see [37] and Waxman and Gavrilets [38] and Bolnick [39]). Evolutionary branching has important consequences for ecological questions of coexistence and Rueffler et al [40] has related environmental feedback dimension to the upper limit for the trait dimension of an evolving population (i.e. feedbacks determine the maximum number of strains that can coexist). Evolutionary branching and its relationship to ecological coexistence is an important and insightful contribution that evolutionary invasion analysis has made but even ignoring branching evolutionary invasion analysis can be a valuable tool in uncovering selection pressures arising due to ecological processes. When there is coexistence of sub-populations the competitive interaction between lineages leads to its own selection pressures so that the basic effect of ecological scenarios is perhaps more apparent when branching is ignored.

1.3 Evolutionary dynamics of infectious disease systems

There is great interest in understanding the evolution of infectious disease characteristics because of the potential for disease management [41]. A key aspect is to understand how ecological scenarios feedback to infectious disease characteristics and how they in turn feedback to ecological densities and the frequencies of phenotypes. These problems are concerned with eco-evolutionary feedbacks and a genetic description, though of great importance elsewhere, may not be necessary in obtaining qualitative descriptions of selection pressures for quantitative polygenic traits. Therefore, evolutionary invasion analysis is a natural framework whenever ecological and evolutionary timescales can realistically be considered separate (but see Day and Proulx [42] and Day and Gandon [43] for an approach that can be used to similar effect when this assumption is not valid). Using an ESS approach Anderson and May [44] demonstrated that parasite virulence can be expected to evolve to intermediate levels and not to benignity (as was previously assumed) due to correlation between transmission and virulence linked to within host pathogen replication rates (this was illustrated empirically for the particular example of Australian myxomatosis). A range of models have developed the theme of how epidemiological dynamics feedback to the evolution of virulence leading to important results. For example, when multiple infections circulate in the host population ESS virulence

depends not only on between host interactions but also on the competitive interactions between parasites within their hosts, and it has been demonstrated that this can select for higher parasite growth rates [18]. Similarly, one can ask how the availability of multiple hosts for an evolving parasite affects selection on the parasite growth rate. Gandon [45] demonstrated that the relative frequencies of the hosts as well as their epidemiological characteristics such as intrinsic host death rate are key to the outcome of evolution in multi-host parasites. The interpretation of these models is potentially important in the management of disease. Studies with direct links to policy include Gandon et al [46] who showed how imperfect vaccines can alter selection pressures on pathogen virulence (imperfect vaccines designed to reduce pathogen toxicity select for high virulence whereas those designed to block infection select against high virulence). Along similar lines in a model where host and parasite share control of disease related mortality (through virulence for the parasite and through tolerance for the host) Miller et al [47] showed that fixed tolerance in the host can alter selection pressures on parasite virulence. In particular, the authors showed that the nature of tolerance and its dependence on growth rate can lead to high or low virulence or even to apparent commensalism. Another focus has been on how epidemiological dynamics feedback to the evolution of resistance with both Antonovics and Thrall [48] and Bowers et al [49] demonstrating that the evolutionary dynamics of resistance are such that hosts with both high and low resistance to the same parasite can coexist. Using a host population consisting of only two strains (perhaps best suited to the resistance alleles of plant pathogen systems) Roy and Kirchner [50] show why this is due to negative frequency dependence between resistance and prevalence in contrast to positive frequency dependence which leads to fixation in the case of tolerance. The likelihood that evolution leads to a dimorphism in resistance phenotypes from an initial monomorphic state was explored by Boots and Haraguchi [19] who showed that the shape of the trade-off between resistance and host reproduction rate determined whether a single value of resistance was a CSS (Continuously Stable Strategy, i.e. an evolutionary equilibrium that is both convergence stable and evolutionarily stable), a branching point or repellor. Taken together, these studies indicate the breadth of results that the eco-evolutionary modelling of infectious disease and host resistance have produced and demonstrate their practical relevance to disease management.

1.4 Thesis outline

The ecologically explicit approach to modelling evolution known as evolutionary invasion analysis provides the tools for deriving analytical expression for singularities and for assessing the evolutionary behavior around singularities. Analytical

results can be verified and illustrated through computer simulations. In this work we take this approach, with, in particular, adaptive dynamics assumptions, and use it to describe the selection pressures underlying epidemiological traits in natural host populations. A key characteristic of the models we study is that they produce endemic rather than epidemic infection dynamics. In our models we use a logistic form for host-birth rate which has two important consequences. It allows for disease dependent population dynamics and therefore parasites are allowed to be associated with an additional mortality effect (and sometimes a fertility reducing effect is additionally included). The logistic form also ensures that the host population is self-regulating (the host would otherwise experience unbounded growth in the absence of the parasite). The ecological (i.e. population dynamic) description of the underlying system is based on continuous ordinary differential equations for susceptible, infected and immune subpopulations of the host. To begin with we give a theoretical introduction to the framework of adaptive dynamics and illustrate it through the established example of the evolution of parasite virulence, see chapter 2. We then extend the results to account for condition dependent virulence which is an interaction between host condition (i.e. host stress) and virulence, that has recently generated much attention from empiricists. Many natural systems are seasonal, potentially leading to seasonal stress, and in chapter 3 we show how to conduct a study for seasonal host populations and analyse its role in the evolution of density dependent virulence. In chapter 4, 5 and 6 we turn our attention to the evolution of resistance. In chapter 4 we begin with a perspective on the relationship between investment in acquired immunity and the lifespan of hosts and parasites. In chapter 5 we derive explicit expressions for optimal investment in the various modes of resistance for a range of epidemiological scenarios. In chapter 6 we elaborate further on the established theory by allowing for parasite diversity and specificity in immune response to the parasites. The results highlight the central role played by specificity in the evolution of host defence. Since our approach throughout has been to build complexity onto a baseline model we conclude our discussion with a short section interpreting established results on the coevolution of virulence and resistance from the perspective of our results on the evolution of virulence and resistance.

Chapter 2

Introduction to adaptive dynamics

Adaptive dynamics is a framework for studying the course of evolution through natural selection. In particular, it considers weak selection through analysis of the viability of rare mutant invaders of a monomorphic resident population which is assumed to be at its dynamic equilibrium. The mutant and resident differ in their phenotypic value for a particular quantitative trait (or traits), denoted here by ω, but otherwise share a common life-history. The prospects of the mutant are captured by its invasion fitness, which is defined as the mutant growth rate when rare, and is here denoted by r. The mutant has positive invasion fitness if $r > 0$ and since it can therefore grow from a rare initial density it will either invade and replace or invade and coexist with the resident depending on the mutual invasibility of the two phenotypes. If $r < 0$, then the mutant is expected to go extinct.

In this manner the population will evolve in the direction of the local selection gradient, $\partial r/\partial\bar{\omega}$ (where the overbar denotes the mutant trait) until an evolutionary singularity is reached. The singularity is therefore an evolutionary steady-state satisfying

$$\frac{\partial r}{\partial \bar{\omega}} = 0 \tag{2.1}$$

The stability properties at the evolutionary steady-state, i.e. whether the population remains at the steady state and whether the population converges to the steady state, depend on second order derivative of the fitness expression. If

$$\frac{\partial^2 r}{\partial \bar{\omega}^2} < 0 \tag{2.2}$$

then the singular strategy is evolutionarily stable. It cannot be invaded by any nearby mutants because it is a maximum with respect to mutants, i.e. neighboring

mutants cannot invade because their invasion fitness will be negative. Evolutionary stability is similar to unbeatable strategies in evolutionary game theory [4] and determines whether the singularity represents a maximum or minimum of invasion fitness over the local set of mutant phenotypes.

A second form of stability for evolving populations is known as convergence stability. It concerns whether or not the evolving population will converge on to the singularity in the first place. In [51] adaptive dynamic assumptions are shown to lead to an ODE for the evolving trait known as the canonical equation of adaptive dynamics. A linear stability analysis of the canonical equation around an evolutionary singularity results in the following condition for convergence stability

$$\frac{\partial^2 r}{\partial \bar{\omega}^2} + \frac{\partial^2 r}{\partial \bar{\omega} \partial \omega} < 0 \tag{2.3}$$

Convergence stability is more similar to traditional notions of mathematical stability in the sense that the singularity is stable to perturbations in the resident phenotype (through say random drift) if it is convergent stable. The condition given by inequality 2.3 is the stabillity condition associated with the canonical equation of adaptive dynamics of [51] which expresses the rate of change of the resident trait in terms of invasion fitness, population size as well as the details of the mutation distribution.

The combination of these two stability terms determines the evolutionary behaviour at the singularity. For example, a singularity that is evolutionarily stable and convergence stable is referred to as a continuously stable strategy (CSS) which is an end-point of evolution. A singularity that is neither evolutionarily stable nor convergence stable is an evolutionary repellor and populations in the locality of a singularity of this nature will evolve away from it. A strategy that is evolutionarily stable but is not convergence stable is known as a Garden of Eden strategy and though such strategies are still unbeatable in the game theoretic sense yet they are not reachable by the evolving population (therefore a CSS is a refinement on the ESS of evolutionary game theory since the latter includes singularities that may not be reachable through the evolutionary process). Finally, if a singularity is convergence stable but not evolutionarily stable, then the population evolves to the singularity (known as a branching point) but then branches initially into two lineages due to disruptive selection.

The adaptive dynamics framework can be extended to encompass coevolution of multiple traits within a population as well as coevolution between populations of different species [51–53]. An important example of a coevolutionary system is the coevolution of parasite virulence and host resistance. Singularities of the coevolu-

tionary process (i.e. co-singularities) correspond to evolutionary steady states of the evolving host and evolving parasite populations. A co-singularity is evolutionary stable if each population satisfies its own evolutionary stability condition. Convergence stability, however, is more complex, because one evolving population influences selection on the other population. In mathematical terms the canonical equation of [51] becomes two dimensional and convergence stability is assessed through a linear stability analysis of the two dimensional system. Denoting host fitness as r with quantitative trait ω_h, and denoting parasite fitness as s with quantitative trait ω_p, convergence stability is determined by the Jacobian [52]

$$\begin{pmatrix} X^*\phi_h(\frac{\partial^2 r}{\partial \bar{\omega}_h^2} + \frac{\partial^2 r}{\partial \bar{\omega}_h \partial \omega}{}_h) & X^*\phi_h \frac{\partial^2 r}{\partial \bar{\omega}_h \partial \omega}{}_p \\ Y^*\phi_p \frac{\partial^2 s}{\partial \bar{\omega}_p \partial \omega}{}_h & Y^*\phi_p(\frac{\partial^2 s}{\partial \bar{\omega}_p^2} + \frac{\partial^2 s}{\partial \bar{\omega}_p \partial \omega}{}_p) \end{pmatrix} \tag{2.4}$$

where ϕ_h and ϕ_p give the speed of mutation of the host and parasite respectively, incorporating the rate and variance of mutation [51]. If the the real part of all of the eigenvalues of the Jacobian are negative, then the co-singularity is convergence stable so that both the host and parasite population will converge on the co-singularity. If the real parts of one or both eigenvalues are positive, then the co-singularity will not be convergence stable. This condition is associated with the two dimensional canonical equation of adaptive dynamics. Linear stability analysis of the canonical system results in the above condition.

2.1 Life history trade-offs

When a beneficial trait, such as resistance, evolves without constraints then evolution is expected to favour organisms with extreme values of that phenotype. Such individuals are known as 'Darwinian demons' i.e. organisms which can maximize any evolving aspect of fitness simultaneously [54] and therefore dominate their niche. Yet traits that are intermediate over a phenotypic range are often observed in nature and in general extreme phenotypic values are rare. One reason that 'Darwinian demons' are not frequently found is that investment in traits is generally costly [55], whether the cost comes as a result of the redeployment of resources from other physiological functions or through pleiotropy (where one gene influences multiple, seemingly unrelated phenotypic traits). Constraints to phenotypic evolution, which are likely to be ubiquitous, are captured by the notion of the trade-off. For example, a trade-off between transmission and virulence in parasite evolution is often asserted and this may often be an example of a trade-off due to pleiotropy since it is based on the assumption that high within host parasite replication rates lead to high trans-

mission and high virulence because of high parasite burden. In host evolution there is likely to be a trade-off between defence and reproduction and this, in contrast, is due to the assumed redeployment of resources from reproductive effort to defensive function.

Trade-offs are essential for evolutionary theory but although evidence for the existence of such trade-offs exist [56, 57], it is not clear what shape we should expect these trade-offs to be. However, there is often a logical basis for assuming diminishing returns, as for example with the evolution of reproductive investment in Myers and Doyle [58] and Heino and Kaitala [59]. In the absence of detailed knowledge as to trade-off shape it is better to work wherever possible with general trade-off functions so that no assumptions are made on the exact form. Occasionally this can be done directly in simple models but more generally geometric methods have been developed that can link the trade-off shape to the evolutionary behavior (for example, the trade-off and invasion plots, TIPS, approach of Bowers et al. [60] and de Mazancourt and Dieckmann [61]'s extension for frequency dependent selection of Levins [62]' fitness set analysis).

We begin by demonstrating the basic analysis and the adaptive dynamics framework in general through the example of the evolution of parasite virulence. The evolution of parasite virulence is an example of a study where general results can be obtained without assuming specific functional forms.

2.2 The evolution of parasite virulence

In an evolutionary context adaptation of a virulence trait is likely to be based on its positive correlation with disease transmission particularly for obligate parasites (see Mackinnon and Read [56], Fenner et al [63] for experimental support and Massad [64], Lenski [65], Bremermann and Pickering [66] for theoretical application). The mechanism underlying this correlation assumes that an increase in parasite replication rate will enhance transmission but also lead to host damage. We therefore assume that an increase in transmission, β, in the parasite is associated with an increase in virulence, α, (i.e. a trade-off between β and α such that $\alpha = \alpha(\beta)$ with such that $\alpha'(\beta) > 0$).

Consider a general model for the density of susceptibles, X, infecteds, Y, and recovereds (immune), Z, in which immunity can wane (an *SIRS* framework). This is represented by the following nonlinear ordinary differential equations

$$\frac{dX}{dt} = aH - qH^2 - bX - \beta XY + \mu Z \tag{2.5}$$

$$\frac{dY}{dt} = \beta XY - (\alpha + b + \gamma)Y \tag{2.6}$$

$$\frac{dZ}{dt} = \gamma Y - (b + \mu)Z \tag{2.7}$$

where the total host density H is the sum of the densities of susceptibles, infecteds and recovereds ($H = X + Y + Z$). All hosts reproduce at rate a, with host self-regulation through a crowding parameter q, which is related to carrying capacity, K, as $K = (a - b)/q$. All offspring are born susceptible (i.e. there is no maternal immunity in the model). Hosts die at natural death rate b. Transmission is a mass action process between susceptible and infected types, with transmission coefficient β. Infected individuals are harmed by their parasite through an additional disease induced mortality rate α. Infected hosts recover to immunity at rate γ, while recovered hosts lose immunity at rate μ.

The non-linearity in this model occurs through the self limitation of host growth and through transmission but may also occur in other epidemiological terms (for example in natural mortality [28] and in disease induced mortality [67]). When there is density dependence in epidemiological terms beyond that of equations 2.5-2.7 evolutionary models based on the maximisation of an infection's basic reproduction number, R_0, may not be accurate. This is because R_0 is derived considering a virgin susceptible environment but more generally the prospects of a mutant parasite will depend on the manner in which the preceding resident has depleted the host environment [41]. The adaptive dynamics approach [31, 32] which explicitly relates ecological dynamics to evolutionary dynamics is more generally accurate and is therefore applied here.

The parasite is maintained at endemic levels when the host-only equilibrium $(X^0, Y^0, Z^0) = ((a-b)/q, 0, 0)$ becomes unstable. Analysis of the eigenvalues shows that the host-only equilibrium loses stability when

$$\frac{\beta X^0}{\alpha + b + \gamma} > 1 \tag{2.8}$$

this is equivalent to the requirement that $R_0 > 1$ for the infection to spread in the host population. The model given by equations 2.5-2.7 is based on vital dynamics (i.e. the birth process is explicitly modelled) and when the host-only equilibrium loses its stability trajectories are attracted to an endemic equilibrium (in contrast

to epidemic models where the host population is assumed constant).

The success of a mutant parasite with mutant values of transmission and hence virulence depends on its invasion fitness, which is the intrinsic growth rate of the sub-population of hosts infected with the mutant parasite in a population of hosts infected with the resident parasite i.e.

$$r = \frac{\dot{Y}}{Y} = \bar{\beta}X - (\bar{\alpha}(\bar{\beta}) + b + \gamma) \tag{2.9}$$

where $\bar{\beta}$ denotes the mutant transmission rate and X is the equilibrium susceptible density at the endemic steady state of the SIRS system which depends on the resident trait β. Through a series of mutation-substitution events, the population will evolve in the direction of the fitness gradient until it reaches the vicinity of the singularity, β^*, where the fitness gradient is zero.

Solving equation 2.1 for the invasion fitness given by equation 2.9 and rearranging indicates that evolutionary singularities satisfy

$$\left.\frac{d(\bar{\beta}X)}{d\bar{\beta}}\right|_* - \left.\frac{d(\bar{\alpha}(\bar{\beta}) + b + \gamma)}{d\bar{\beta}}\right|_* = 0 \tag{2.10}$$

$$\Leftrightarrow \left.\frac{d\bar{\alpha}}{d\bar{\beta}}\right|_* = \left.\frac{d(\bar{\beta}X)}{d\bar{\beta}} \Big/ \frac{d(\bar{\alpha}(\bar{\beta}) + b + \gamma)}{d\bar{\alpha}}\right|_* \tag{2.11}$$

$$= \left.\frac{B}{C}\right|_* = \frac{X^*}{1} \tag{2.12}$$

where the numerator in the right hand side of equation 2.11 represents the benefit to the parasite of a mutation (due to the increase it brings in transmission rate) and is therefore denoted by B in equation 2.12. Similarly the denominator in equation 2.11 represents the cost to the parasite of a mutation (due to the increase it brings in virulence rate) and is denoted C. The left hand side of equation 2.11 corresponds to the gradient of the trade-off between transmission and virulence at which the singularity lies. As a consequence of virulence increasing more rapidly than transmission as parasite investment increases (i.e. as a consequence of diminishing returns) any increase in the right hand side of equation 2.12 results in the location of the singularity shifting to high values of mutant transmission, see figure 2.1 for a graphical illustration. This implies that singular transmission-virulence is a cost benefit analysis if there are diminishing returns on investment, so that optimal parasite investment, ψ^*, is high whenever the benefit is large relative to the cost,

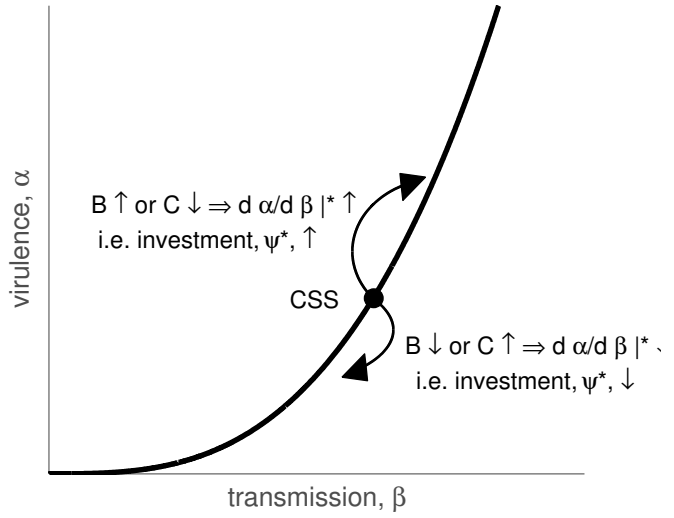

Figure 2.1: *Geometric explanation of the cost benefit analysis of parasite transmission.* A singularity is located on the trade-off between parasite transmission, β, and virulence, α according to the equation $d\bar{\alpha}/d\bar{\beta}|_* = B/C|_*$. When diminishing returns on parasite investment in transmission are assumed (i.e. a negatively curved trade-off) then investment is proportional to the ratio of benefit of transmission to the cost of virulence.

i.e.

$$\psi^* \propto \left.\frac{B}{C}\right|_* = X^* \tag{2.13}$$

The evolutionary outcome at the singularity depends on two criteria: evolutionary stability (ES, whether the strategy is a local fitness maximum or minimum), requiring for a fitness maximum that

$$\left.\frac{\partial^2 r}{\partial \bar{\beta}^2}\right|_{\bar{\beta}=\beta=\beta^*} < 0 \;\Rightarrow\; \left.\bar{\alpha}''(\bar{\beta})\right|_{\bar{\beta}=\beta=\beta^*} > 0 \tag{2.14}$$

and convergence stability (CS, whether the strategy is locally attracting or repelling) [32], requiring for a local attractor that

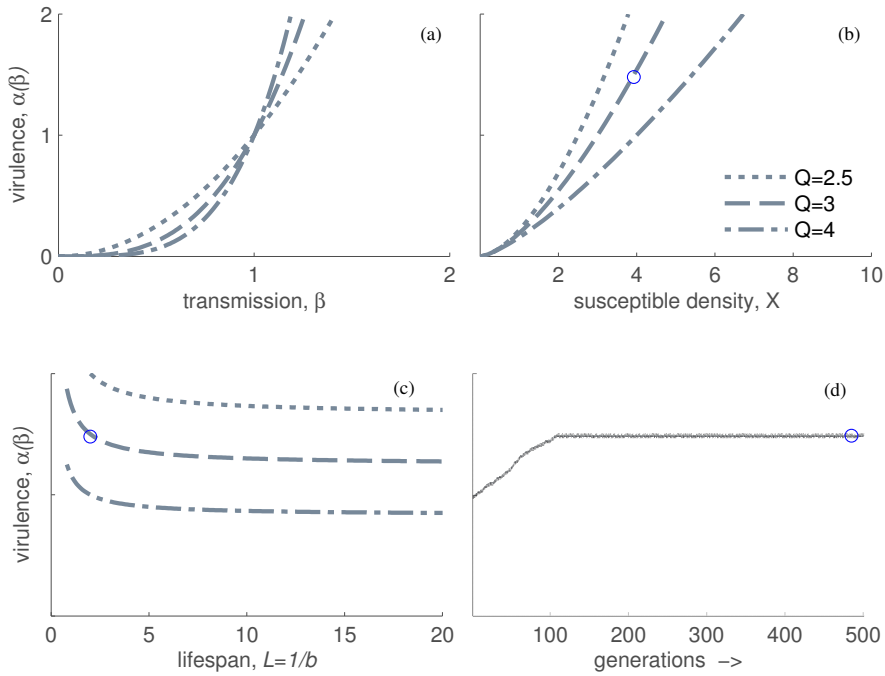

Figure 2.2: *CSS parasite investment in transmission associated with a cost of increased virulence.* In (a) the various trade-off shapes are shown. In (b) the relationship between CSS investment and equilibrium susceptible density, X, is illustrated. In (c) the relationship between CSS investment and host lifespan, $L = 1/b$, is illustrated. In both (b) and (c) open circles represent the final level of evolved resistance from ODE simulations of the evolutionary process. In (d) the simulation itself is illustrated with a single parasite lineage converging on a CSS represented by a blue circle. The blue circle in (d) corresponds to the same value of virulence as the blue circles in (b) and (c) which demonstrates that the theoretical prediction matches the simulation result. The virulence-transmission trade-off was $\alpha(\beta) = \beta^Q$, where $Q > 1$, i.e. a trade-off with accelerating costs which leads to a CSS. Parameters were: $\mu = 0, \beta = 1, \alpha = 4$.

$$\left(\frac{\partial^2 r}{\partial\bar{\beta}\partial\beta} + \frac{\partial^2 r}{\partial\bar{\beta}^2}\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{2.15}$$

$$\Rightarrow \left(\frac{\partial X}{\partial\beta} - \bar{\alpha}''(\bar{\beta})\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{2.16}$$

$$\Leftrightarrow \left(\frac{\alpha' - X}{\beta} - \bar{\alpha}''(\bar{\beta})\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{2.17}$$

$$\Leftrightarrow \bar{\alpha}''(\bar{\beta})\Big|_{\bar{\beta}=\beta=\beta^*} > 0 \tag{2.18}$$

where equation 2.18 follows from equation 2.17 because $d\bar{\alpha}/d\bar{\beta}|_* = X$ from equation 2.11.

Equation 2.14 and equation 2.18 are equivalent so the singularity is either both ES and CS (i.e. a CSS) or neither ES nor CS (i.e. a repellor) depending on the curvature of the trade-off. The singularity described by equation 2.12 is a CSS for any trade-off shape that follows an accelerating cost structure (i.e. diminishing returns). We illustrate this by specifying a particular form for the trade-off, see figure 2.2 a. Solving equation 2.1 (using symbolic computation) provides continuous curves for the dependence of CSS investment on susceptible density and for the dependence of CSS investment on host lifespan, see figure 2.2 $b - c$ respectively.

2.3 Simulation of the evolutionary process

Simulations, with deterministic population dynamics but with random mutations provide illustration of the theoretical predictions for a particular parameter set, see figure 2.2 (d). In the simulation (and in the simulations presented throughout this work) the population dynamics of the system given by equations 2.5-2.7 are solved with ODE-solvers so that the asymptotic behavior of the ecological system can be determined [68]. A mutant type is generated as a small deviation around the current resident trait (i.e. the mutant is randomly assigned a slightly higher or slightly lower trait value than the resident) and is introduced at low density into the equilibrium resident population. The population dynamics for the resident-mutant system initially composed of an equilibrium density of residents and a low density of mutants is then solved for a further period of time until the asymptotic behavior can be determined. Here one of three outcomes is possible, the mutant may fixate in the population competitively excluding the resident, the resident may exclude the mutant or the resident and mutant may coexist at equilibrium so that evolutionary branching, which can lead to dimorphism or polymorphism, has occurred, see algorithm 1 for an algorithmic description of the simulation process. In figure 2.2 (d), the adaptive dynamics process leads to a sequence of successful and failed invasions which leads to the convergence of a parasite lineage on a CSS value of virulence represented by an open circle. The open circles in figure 2.2 $(b) - (d)$ demonstrate that the theoretical prediction is in accordance with the simulation outcome.

2.4 Discussion

Equation 2.13, which was derived assuming accelerating costs, demonstrates that parasite investment in transmission (and therefore virulence) at the evolutionary steady state is proportional to the density of susceptible hosts. Equations 2.14 and

Algorithm 1: Monomorphic simulation of the evolutionary process for non-periodic life-history and epidemiological rates

1. Define a real-valued vector, V, of length $n+2$ to represent n densities of infected hosts, I_j for $j = 1..n$, who are infected by distinct parasite strains with phenotypic values on a transmission-virulence trade-off, as well as a susceptible host density, S, and immune host density, R, i.e. $V = \{I_j, S, R\}$ for $j = 1..n$
2. Set the value of one of the infected classes in the vector to an initial real number I_0, i.e. $I_k = I_0$
3. Solve the population dynamics using an ODE-solving algorithm for the SI_kR model with initial conditions $S_0 = (a-b)/q$ and I_0 until $I_{T+\Delta T} - I_T < \Delta I$ for arbitrarily small ΔT and ΔI (ensure ΔT is sufficiently big and ΔI sufficiently small so that the algorithm does not terminate during cyclic transients)
4. If $I_{T+\Delta T} < I^{extinct}$ where $I^{extinct}$ is very small ($I^{extinct} = 10^{-4}$ throughout this work) terminate algorithm with error 'disease extinction' otherwise make the final values from step 3 the host environment as set by the resident strain, r, i.e. set $I_0^r = I_{T+\Delta T}$ and $S_0 = S_{T+\Delta T}$ and $R_0 = R_{T+\Delta T}$
5. Draw a random number to determine whether it is the next or the previous element in the vector that is to represent the mutant strain, m, i.e. $I_{k-1} = I^m$ or $I_{k+1} = I^m$
6. Set the value of I^m to a positive real number $I_0^m < I_{rare}$, where I_{rare} is arbitrarily small
7. Solve the population dynamics using an ODE-solving algorithm for the SI^rI^mR model with initial conditions $\{S_0, I_0^r, I_0^m, R_0\}$
8. Terminate solver once $I_{T+\Delta T}^r - I_T^r < \Delta I$
9. If $I_{T+\Delta T}^r < I^{extinct}$ then set $I_0^r = I_{T+\Delta T}^m$ and $S_0 = S_{T+\Delta T}$, $R_0 = R_{T+\Delta T}$ and print 'mutant becomes resident'. If $I_{T+\Delta T}^m < I^{extinct}$ then set $I_0^r = I_{T+\Delta T}^r$ and $S_0 = S_{T+\Delta T}$, $R_0 = R_{T+\Delta T}$ and print 'mutant is extinct'. If $I_{T+\Delta T}^r < I^{extinct}$ and $I_{T+\Delta T}^m < I^{extinct}$ terminate algorithm with error 'evolutionary suicide has occurred'. Otherwise terminate algorithm with error 'branching point has been reached'
10. Repeat steps 5-9 for a fixed number of generations

2.18 show that the assumption of accelerating costs always leads to a CSS. Because equilibrium susceptible density is an increasing function of natural mortality (i.e. $X = (\alpha + b + \gamma)/\beta$) we can therefore expect to find high rates of exploitation for parasites of short-lived hosts (i.e. this leads to the prediction that parasites of short lived hosts will tend to be adapted to exploit their hosts more intensely). This is an important observation that is often explained as a selection pressure existing for the parasite to exploit the host strongly if it is going to die quickly anyway. However, the adaptive dynamics approach makes it very clear that in fact the relative benefit of investment in exploitation depends on the susceptible density, for if this density is low then the increased transmission rate is futile. Therefore the only relevance of high natural mortality rate is that it corresponds to a higher susceptible density and

in that case transmission works more efficiently so that high investment is worthwhile. The evolution of parasite virulence is relatively straightforward and simple to understand because of the simplicity of the invasion fitness. However, the inclusion of further density dependence and the incorporation of seasonality in populations dynamics makes the evolutionary dynamics more challenging to understand. We include these details and examine their impact on the outcome of evolution in chapter 3.

Chapter 3

Evolution of density dependent virulence

3.1 Preface

The material in this chapter corresponds to the following 2013 publication,

Donnelly, R., Best, A., White, A. and Boots, M., 2013 Seasonality selects for more acutely virulent parasites when virulence is density dependent, *Proceedings of the Royal Society B-Biological Sciences*, **280**, 20122464.

I was lead author for this publication.

3.2 Introduction

Parasites by definition cause host damage and understanding how parasite virulence evolves is key to disease management [41, 44]. As a consequence there is a substantial theoretical literature that has explored the effects of epidemiological characteristics on the evolution of virulence, defined in this literature as parasite-induced mortality [44, 66, 69, 70]. Recent empirical work has emphasised that virulence is likely to be context dependent, with the lethality of infection contingent on factors such as host nutritional status, oxygen availability or temperature [71–73]. Clearly a key factor in determining this context is host density leading to the potential for density dependent virulence (DDV).

Host density can influence disease incidence and severity in a number of ways [74–76]. Poor condition can alter the likelihood of transmission [74], however, the effect is system specific if present at all [75]. The field survey of Lively *et al.* [77] in *Impatiens capensis* infected with the rust *Puccinia recondita*, for example, revealed that the proportion of plants that were infected was not related to density, but that the effect

of infection on plant growth was more severe under high host density (i.e. *DDV* was present). Furthermore, a recent in situ experiment [78] reported *DDV* in oomycete infected seedlings of the Neotropical tree, *Sebastiana longicuspis*; and in general *DDV* seems to be widespread in plant disease [75, 76]. In animals, several papers report findings that relate host starvation to disease induced mortality [72, 79, 80]. As a whole this work emphasises the importance of condition to virulence in a diverse range of systems.

Despite being increasingly recognised in empirical studies, the impact of *DDV* on disease dynamics has received relatively little theoretical attention. Anderson and May [12] briefly explore the consequences of density-dependent pathogenicity to invasion thresholds in systems with linear host growth. The linearity of host growth makes parasite limitation of host growth the focus and it is concluded that the virulence rate is critical to parasite regulation of the host population in the basic model, but with *DDV* the transmission rate is also key. Lively [81] developed a population dynamic model with density dependent regulation of birth where the density dependent component was amplified due to infection. His results showed that an infection appearing benign at low density can be effectively castrating at the higher equilibrium density. This emphasises the importance of considering parasite evolution in its ecological context - which will often include population cycles. Seasonality, a cause of such cycles, is well known to have a profound impact on human and wildlife disease epidemiology [22, 82–84] but has rarely been considered in evolutionary models. The evolution of the sensitivity to seasonality [85] and how seasonality may contribute to the evolution of the parasite life-cycle have been examined [86]. Since seasonality may lead to density fluctuations, an exploration of the role of *DDV* in infectious disease systems subject to fluctuating host abundance will provide novel insight into the evolution of virulence. We therefore develop evolutionary models where *DDV* acts to increase disease induced mortality as host density increases and where hosts are subject to a fluctuating birth rate. We apply modern evolutionary game theory (adaptive dynamics; Geritz et al. [31], Metz et al. [32]) to assess the evolutionary epidemiology of this system as the amplitude of seasonality increases.

3.3 Methods and Results

3.3.1 Model Framework

We develop a model for the density of susceptibles, X, infecteds, Y, and recovereds (immune), Z, in which immunity can wane (an *SIRS* framework). This is

represented by the following nonlinear ordinary differential equations

$$\frac{dX}{dt} = aH(1 - qH) - bX - \beta XY + \mu Z \tag{3.1}$$

$$\frac{dY}{dt} = \beta XY - (\alpha(1 + cH) + b + \gamma)Y \tag{3.2}$$

$$\frac{dZ}{dt} = \gamma Y - (b + \mu)Z \tag{3.3}$$

where the total host density H is the sum of the densities of susceptibles, infecteds and recovereds ($H = X + Y + Z$). All hosts reproduce at rate a, with host self-regulation through a crowding parameter q, which is related to carrying capacity, K, as $K = (a-b)/aq$. All offspring are born susceptible. Hosts die at natural death rate b. Transmission is a mass action process between susceptible and infected types, with transmission coefficient β. High host density, associated with increased scarcity of resources, can lead to increases in disease induced mortality [77] and therefore we assume infected hosts are subject to both some baseline virulence rate, α, and a density-dependent component, $c\alpha H$, where c scales the impact of density on virulence. Infected hosts recover to immunity at rate γ, while recovered hosts lose immunity at rate μ.

The parasite is maintained at endemic levels when the host-only equilibrium $(\hat{X}, \hat{Y}, \hat{Z}) = ((a - b)/aq, 0, 0)$ becomes unstable. Analysis of the eigenvalues shows that the host-only equilibrium loses stability when

$$\beta > c\alpha + \frac{\alpha + b + \gamma}{\hat{X}} \tag{3.4}$$

therefore, increasing the strength of density-dependent virulence makes it harder for the parasite to invade, requiring a greater transmission rate.

3.3.2 Parasite Evolution

In an evolutionary context adaptation of a virulence trait is likely to be based on its positive correlation with disease transmission particularly for obligate parasites (see Mackinnon and Read [56], Fenner et al [63] for experimental support and Massad [64], Lenski [65], Bremermann and Pickering [66] for theoretical application). The mechanism underlying this correlation assumes that an increase in parasite replication rate will enhance transmission but also lead to host damage. We therefore assume that an increase in transmission, β, in the parasite is associated with an increase in baseline virulence, α, (i.e. a trade-off between β and α such that $\alpha = \alpha(\beta)$ and such that $\alpha'(\beta) > 0$) and that total virulence is amplified as density increases

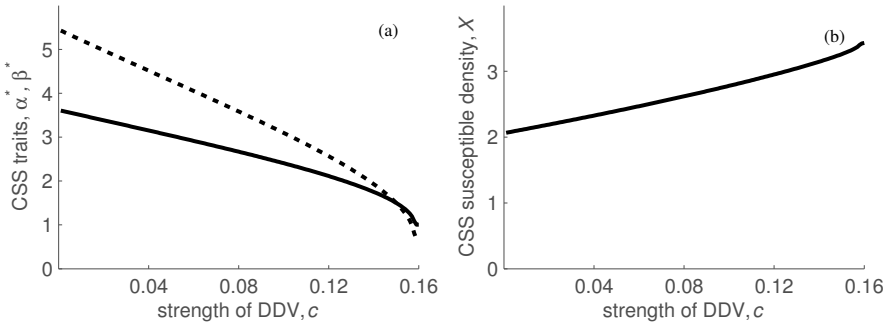

Figure 3.1: *Evolutionary results for the non-seasonal* SIRS *model with* DDV. Results given as a function of the strength of *DDV*. (a) *CSS* trait values for transmission, β (solid line –), and parasite virulence, α (dots $\cdots$); (b) endemic susceptible equilibrium density taken along the CSS. Parameters: $a = 5, b = 1, q = 0.1, \gamma = 1, \mu = 1$. Trade-off details: $7-6.5\frac{(1.259-0.29\beta)}{(1.039-0.04317\beta)}$, i.e. a trade-off where each incremental increase in transmission incurs weakly accelerating costs in the form of increased virulence.

through *DDV*. Evolutionary models based on the maximisation of an infection's basic reproduction number, R_0, may not be accurate when density dependence is present in epidemiological terms [41]. The recent framework of adaptive dynamics [31, 32] which explicitly relates ecological dynamics to evolutionary dynamics is more appropriate since we are investigating the implication of *DDV*, a density dependent epidemiological term at the ecological scale, to the evolution of parasites. This method assumes a separation of evolutionary and ecological time-scales - an assumption not always valid for epidemiological systems [87]. However, simulations where mutations are allowed to occur before the ecological attractor has been reached, have often confirmed the qualitative robustness of results to a relaxation of this assumption (see e.g. Geritz et al [88]). Taking this approach we assume a rare mutant with a slightly different phenotypic value of the adaptive trait (here virulence) attempts to invade a resident population at equilibrium.

The success of the mutant depends on its invasion fitness, given by

$$r = \bar{\beta}X - (\bar{\alpha}(\bar{\beta})(1 + cH) + b + \gamma) \tag{3.5}$$

where $\bar{\beta}$ denotes the mutant transmission rate and X, H are the equilibrium densities at the endemic steady state of the SIR system which depends on the resident trait β. If $r > 0$ then the mutant parasite will invade to coexist with or replace the resident. Through a series of mutation-substitution events, the population will evolve in the direction of the fitness gradient until it reaches the vicinity of the singularity, β^*, where the fitness gradient is infinitesimal.

Singularities therefore satisfy

$$\left.\frac{\partial r}{\partial \bar{\beta}}\right|_{\bar{\beta}=\beta=\beta^*} = \left.\left(X - \bar{\alpha}'(\bar{\beta})(1+cH)\right)\right|_{\bar{\beta}=\beta=\beta^*} = 0 \tag{3.6}$$

The evolutionary outcome for a singularity depends on two criteria: evolutionary stability (ES, whether the strategy is a local fitness maximum or minimum), requiring for a fitness maximum that

$$\left.\frac{\partial^2 r}{\partial \bar{\beta}^2}\right|_{\bar{\beta}=\beta=\beta^*} < 0 \;\Rightarrow\; \left.\alpha''(\bar{\beta})(1+cH)\right|_{\bar{\beta}=\beta=\beta^*} > 0 \tag{3.7}$$

and convergence stability (CS, whether the strategy is locally attracting or repelling) [32], requiring for a local attractor that

$$\left.\left(\frac{\partial^2 r}{\partial \bar{\beta}\partial\beta} + \frac{\partial^2 r}{\partial \bar{\beta}^2}\right)\right|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{3.8}$$

$$\Rightarrow \left.\left(\frac{\partial X}{\partial \beta} - \bar{\alpha}'(\bar{\beta})c\frac{\partial H}{\partial \beta} - \alpha''(\bar{\beta})(1+cH)\right)\right|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{3.9}$$

To examine how the singular transmission rate, β^*, varies for changes in other parameters (and therefore how the singular value of baseline virulence, α^*, varies) we choose a trade-off such that the singular point is a continuously stable strategy (CSS), i.e. ES and CS, which is an attracting endpoint for evolutionary trajectories (see figure 3.1 legend for the exact form of the trade-off). By equation (3.7) this requires $\alpha''(\beta) > 0$, corresponding to accelerating costs of transmission.

Figure 3.1a shows the behaviour as the strength of *DDV*, c, is increased, indicating that the parasite decreases investment in transmission as the density-dependence increases. We have repeated this analysis for a wide range of parameter values and find the pattern to be qualitatively robust to parameter and trade-off choice (though accelerating costs through virulence of increased transmission are required). Furthermore, it can be shown that the decrease in *CSS* virulence follows directly from the increase in susceptible density, see *Appendix A* and figure 3.1.

Investment in transmission as functions of the other demographic and epidemiological parameters can be understood from considering the fitness gradient, equation (3.6), which locates the singularity position at the trait satisfying $\alpha'(\beta^*) = X(\beta^*)/(1+cH(\beta^*))$. Higher values of $\alpha'(\beta^*)$ correspond to higher evolved transmission and virulence. The term $X(\beta^*)/(1+cH(\beta^*))$ which fixes the singularity location is composed of a numerator and denominator, reflecting two opposing se-

Figure 3.2: *Evolutionary results for the non-seasonal* SIRS *model with* DDV *as demographic and epidemiological parameters are varied. CSS* parasite virulence as a function of (a) birth rate, (b) host natural mortality rate, (c) rate of waning immunity, (d) recovery rate and (e) the crowding parameter. When not varied in the individual figures above, parameters are as in figure 3.1 except the strength of *DDV* which is fixed ($c = 0.15$) so that baseline virulence and *DDV* contribute approximately equal amounts to total virulence.

lective forces. According to the numerator parameter values that decrease (increase) the susceptible density select for lower (higher) transmission, but simultaneously, according to the denominator, those same values may lead to a decrease (increase) in total host density which selects for higher (lower) transmission because of its effect on *DDV*. Figure 3.2a-e demonstrates that the balance of these selective forces favours an increase in *CSS* virulence for an increase in all parameters except the birth rate, a.

Where an evolutionary singularity has convergence stability but not evolutionary stability, the population will find itself at a fitness minimum, undergo disruptive selection and branch in to two distinct strains. In this model, however, despite the additional density dependence the conditions for this cannot be met and branching cannot occur (see *Appendix B* for details and *Appendix C* for branching in a related model).

3.3.3 Model Incorporating Seasonality

To induce fluctuations in the population dynamics we introduce a seasonally forced reproduction rate of intensity δ so that $a = a(t)$.

We present results based on a sinusoidal forcing function $a(t) = a_0(1+\delta sin(2\pi t/\epsilon))$, following previous studies [12, 89], where $\delta \in [0, 1]$ is the amplitude and ϵ is the period of the seasonal forcing which has an average value of a_0. $\delta = 1$ is the maximum amplitude that can be attained without a negative reproduction rate while $\delta = 0$ corresponds to a constant reproduction rate (no seasonality).

To emphasize the importance of *DDV* let us first consider the standard SIRS model without *DDV* with $a = a(t)$. This corresponds to our model when $c = 0$. The population dynamics will converge to either a periodic attractor or a chaotic attractor [89]. When the dynamics are periodic the invasion fitness of the system over a period, of length T, from P_0 to P_1 [90], where $P_1 = P_0 + T$, is:

$$r = \frac{1}{T}\int_{P_0}^{P_1} (\bar{\beta}X(t) - (\bar{\alpha}(\bar{\beta}) + b + \gamma))dt \tag{3.10}$$

with $\bar{\beta}$ denoting the mutant parameter value. We show in *Appendix D* that the singularity position is unaffected by seasonality for the classical *SIRS* model with periodic dynamics (it can be similarly shown for chaotic dynamics) and this finding has been verified by simulation of the evolutionary process (see White et al [91] for an explanation of the simulation process). The proof in *Appendix D* rests on the fact that the average density of susceptibles over a period is constrained to be constant with respect to the magnitude of seasonality, δ, and the period of the forcing, ϵ,

$$\frac{1}{T}\int_{P_0}^{P_1} X(t)dt = \frac{\alpha + b + \gamma}{\beta} \tag{3.11}$$

The CSS remains invariant under seasonality when other parameters such as transmission are forced and this applies also to other models beyond the standard *SIRS*, see *Appendix E*. Therefore, a key result is that in infectious disease systems that do not include *DDV*, the amplitude and period of seasonality will not alter the evolutionary end-point of virulence.

3.3.4 Population dynamics of the *SIRS* model with *DDV* under seasonality.

Under *DDV* ($c > 0$), average susceptible density is no longer conserved. Now

$$\frac{1}{T}\int_{P_0}^{P_1} X(t)dt = \frac{\alpha + b + \gamma}{\beta} + \frac{\alpha c}{\beta}\frac{1}{T}\int_{P_0}^{P_1} H(t)dt \tag{3.12}$$

and the average susceptible density depends on the average total host density which itself may depend on the magnitude of seasonality, δ. Due to complexity of the problem, we cannot analytically find the average population densities needed to show the effect of seasonality on a CSS. Instead, the average densities are calculated numerically. We use the trade-off of section 3.3.2 (see caption of figure 3.1a) between baseline virulence and transmission so that the singularity, when $\delta = 0$, is a CSS. Numerically calculated total population densities over a period show that both average susceptible density and average total host density decrease as δ increases, figure 3.3a. We have verified that this pattern is consistent across parameter space for periods within reasonable bounds (we assume this is less than one hundred times, and more than one hundredth of, the infectious period) and for parameters that maintain infection within the host population for $\delta \in [0, 1]$.

3.3.5 Parasite evolution under seasonality.

For our seasonal model the invasion fitness is

$$r = \frac{1}{T}\int_{P_0}^{P_1} (\bar{\beta}X(t) - (\bar{\alpha}(\bar{\beta})(1 + cH(t)) + b + \gamma)dt \tag{3.13}$$

and applying the singularity condition $\frac{\partial r}{\partial \bar{\beta}} = 0|_{\bar{\beta}=\beta}$ implies

$$\alpha'(\beta) = \frac{\int_{P_0}^{P_1} X(t)dt}{\int_{P_0}^{P_1} (1 + cH(t))dt} \tag{3.14}$$

$$= \frac{\alpha}{\beta} + \frac{b+\gamma}{\beta}\frac{1}{(1 + \frac{c}{T}\int_{P_0}^{P_1} H(t)dt)} \tag{3.15}$$

where substitution of equation (3.12) into equation (3.14) results in equation (3.15). Thus, the value of the CSS, α^*, is fixed by the average total host density over the period. Referring back to the population dynamics shown in figure 3.3a, since average total population density decreases with increasing amplitude of seasonality (and does so across the parameter space) the right hand side of equation (3.15) is increasing with δ. We therefore expect that the CSS value will increase with the amplitude of seasonality. To verify this we numerically locate the position of the CSS using equation (3.14) for various values of δ, see figure 3.3b, which confirms that selection favors an increased investment in transmission as the amplitude of seasonality increases. The CSS values are also confirmed using simulations of the adaptive dynamics process (see White et al [91] for an explanation of the simulation process). Furthermore, the increase in virulence that evolves as a result of seasonality in the SIRS system with DDV, depends on the nature of the infection with chronic

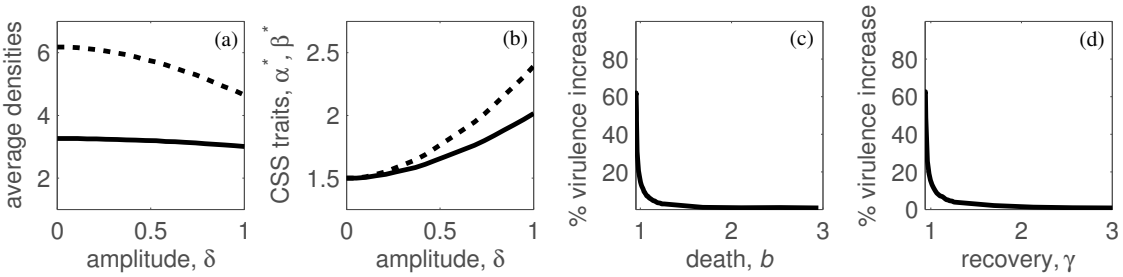

Figure 3.3: *Evolutionary results for the* SIRS *model with seasonally forced host reproduction and with* DDV. (a) Total overall host density (dots $\cdots$) and susceptible density (solid line -) over a period for varying amplitudes of seasonality, δ; (b) CSS trait values for transmission (solid line -) and virulence (dots $\cdots$) for varying amplitudes of seasonality, δ. (c) Percentage increase in CSS virulence (difference between CSS virulence in the non-seasonal model and CSS virulence when the amplitude of seasonality is 0.5) for varying natural mortality rate, and for varying recovery rate in (d), representing varying nature of infection along the chronic/acute spectrum. Here the strength of DDV is again fixed ($c = 0.15$); see figure 3.1 for all other parameter values.

infection or long-lived hosts (low γ, low b) as opposed to acute infection or short-lived hosts (high γ, high b) having the greatest percentage increase in virulence under seasonality (figure 3.3c and d). Seasonality therefore has a larger impact on virulence evolution (in the SIRS model with DDV) as the infective period increases.

3.4 Discussion

We have developed a series of models that examine the impact of density dependent virulence (DDV) on the evolution of parasites in both seasonal and non-seasonal environments. Our results may be important in a wide range of natural disease systems because an interaction between host stress and cost of infection, captured here by DDV, is likely to be common [74, 76]. We show firstly that parasites are selected to lower exploitation and therefore lower transmission and virulence as the strength of DDV increases. Our second key result is that seasonal forcing of systems incorporating DDV leads to an increase in exploitation and therefore higher transmission and virulence, with the impact of seasonality more pronounced for longer infection periods. As such our models emphasise both the importance of context dependence and seasonality in the evolution of parasites.

Under the assumptions of the trade-off hypothesis high transmission follows from intense host exploitation, the fitness gain of which must be counted against a short infectious period associated with severe parasite induced mortality [64, 66]. Theory has shown that intermediate parasite virulence is often favoured when the ensuing trade-off is saturating [18, 69, 92]. The virulence that evolves is that which optimises parasite fitness and thus under the trade-off hypothesis it can depend directly on host exploitation strategy, demographic and epidemiological rates. Here, with the inclusion of DDV, optimal fitness also depends indirectly on these rates through their effect on total host density. We find that decreased virulence is selected for as the strength of DDV increases. This is in contrast to increasing natural mortality (and recovery) that leads to the evolution of higher host exploitation (here and in the models of Williams and Day [70], May and Anderson [93], Kakehashi and Yoshinaga [94], Choo et al [95]). This is an important insight from our models; DDV has the opposite effect on the evolution of parasites to that of higher baseline mortality. It emphasises the importance of ecological feedbacks in understanding the evolution of virulence. Other theoretical studies on the evolution of virulence [96, 97] have found that frequency dependent transmission leads to qualitatively similar results to the density dependent case. Here, however, qualitatively different results were found to be possible in our model when the transmission is frequency dependent (results not included). In particular CSS virulence was found to increase when the trade-off between virulence and transmission was weakly convex.

When seasonality in host birth is included in classical epidemiological models with DDV we show that the result is an increase in evolved virulence. This outcome is rooted in the effect of the DDV interaction on the average population densities over the seasonal period. In a range of classic baseline models (e.g. $SIRS$ and variants) lacking this extra density dependence, the average susceptible population

density in the fitness expression over a period of any type of forcing (and for a multiplicity of forced terms) remains constant with respect to the magnitude of seasonality. Hence, deterministically, the evolution of virulence is unchanged by seasonality except when density dependence acting on virulence or recovery breaks the invariance of the average susceptible population density. This is consistent with the results of Williams and Dye [98] where R_0 for the classical *SIR* model with seasonal transmission was found to be independent of the amplitude of seasonality.

The effect of seasonality on the evolution of virulence was previously associated with the intuition that periods of low density ought to purge those parasites with more virulent strategies. This is a stochastic argument based on the most virulent parasites showing the greatest vulnerability to stochastic extinction during the periods of low population density. The deterministic effect, hitherto ignored, when DDV is present, is a marked increase in evolved virulence. Jokela *et al.* [72] discuss the intuition when they examine how anoxic conditions and starvation of hosts affect virulence of two closely related trematode parasites, *Rhipidocotyle campanula* and *R. fennica*, of the freshwater clam, *Anodonta piscanalis* (sampled from temperate lakes in Finland). Seasonal starvation and anoxia in these Finnish lakes were implicated in stress dependent virulence which was found to be prevalent in all populations. Contrary to the hypothesis that seasonality should lead to lower exploitation strategies through a purging of more virulent strains, high virulence was observed in multiple populations of *Rhipidocotyle campanula*. The authors suggest that this may be due to eradication of the infection from the clam population in periods of high stress and repopulation from refugia of infection in a separate host species. Here, our theoretical results offer an alternative explanation, since acute virulence is predicted by our models under the similar conditions of seasonal *DDV*.

In a related model assuming evolving baseline virulence but this time with non-evolving *DDV*, evolutionary branching has the potential to occur (see *Appendix C*). The requisite condition for branching of two strategies as proposed in Heino et al [99] (see also Rueffler et al [40]), namely a feedback dimension (to per capita growth of infecteds) of two, is present in this model. This is reminiscent of branching found in an *SI* type model when density dependent natural mortality is included (Svennungsen and Kisdi [100] which is an extension of Pugliese [101]; see also Best et al [102]). The result extends the range of disease models for which branching has been demonstrated; amongst which already are counted models incorporating density dependent death [100, 101], superinfection [103, 104], 'specialist' parasitism [105–107] and selective predation [108]. When *DDV* evolves together with baseline virulence in our main model, however, and both population feedbacks have adaptive traits, mutual invasibility becomes impossible and no branching can occur.

To conclude our models emphasise the importance of context dependency and

seasonality in the evolution of infectious disease. In particular we highlight the need for both experimentalists and theoreticians in evolutionary epidemiology to allow for the possibility of a density dependent virulence, as theory predicts its presence may significantly alter the evolutionary outcome of such systems.

Appendix A

Response of susceptible density to parameter changes drives change in CSS trait value

The equation for the location of the singularity is

$$\left.\frac{\partial r}{\partial \bar{\beta}}\right|_{\bar{\beta}=\beta=\beta^*} = \left(X - \bar{\alpha}'(\bar{\beta})(1+cH)\right)\Big|_{\bar{\beta}=\beta=\beta^*} = 0 \tag{A.1}$$

where the invasion fitness, r, is given by equation (3.5) - *main text*. The infecteds ODE is

$$\frac{dY}{dt} = \beta XY - (\alpha(1+cH) + b + \gamma)Y \tag{A.2}$$

Differentiating equation (A.1) with respect to the strength of DDV, c, combining with equilibrium total host density from equation (A.2), its derivative with respect to c, and equation (A.1) leads to

$$\left.\frac{\partial}{\partial c}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}}\right|_{\bar{\beta}=\beta=\beta^*} = -\frac{\partial X}{\partial c}\left.\frac{(b+\gamma)}{\alpha(1+cH)^2}\right|_{\bar{\beta}=\beta=\beta^*} \tag{A.3}$$

analogously

$$\frac{\partial}{\partial a}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}} = -\frac{\partial X}{\partial a}\frac{(b+\gamma)}{\alpha(1+cH)^2} \tag{A.4}$$

$$\frac{\partial}{\partial \mu}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}} = -\frac{\partial X}{\partial \mu}\frac{(b+\gamma)}{\alpha(1+cH)^2} \tag{A.5}$$

$$\frac{\partial}{\partial q}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}} = -\frac{\partial X}{\partial q}\frac{(b+\gamma)}{\alpha(1+cH)^2} \tag{A.6}$$

$$\frac{\partial}{\partial b}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}} = -\frac{\partial X}{\partial b}\frac{(b+\gamma)}{\alpha(1+cH)^2} + \frac{X}{\alpha} \tag{A.7}$$

$$\frac{\partial}{\partial \gamma}\frac{\partial \bar{\alpha}}{\partial \bar{\beta}} = -\frac{\partial X}{\partial \gamma}\frac{(b+\gamma)}{\alpha(1+cH)^2} + \frac{X}{\alpha} \tag{A.8}$$

where equations (3.1-3.3) are all evaluated at $\beta = \bar{\beta} = \beta^*$.

From equation (A.3) it is clear that $\frac{\partial}{\partial c}\frac{\partial \alpha}{\partial \bar{\beta}}$ is sign-equivalent to $-\frac{\partial X}{\partial c}$. Analysis indicates that $\frac{\partial X}{\partial c} > 0$ for a wide range of random parameter values and it therefore follows that $\frac{\partial}{\partial c}\frac{\partial \alpha}{\partial \bar{\beta}} < 0$, see *main text* figure 3.1a. Similarly this holds for host reproduction, a.

From equation (A.5) it is clear that $\frac{\partial}{\partial \mu}\frac{\partial \alpha}{\partial \bar{\beta}}$ is sign-equivalent to $-\frac{\partial X}{\partial \mu}$. Analysis indicates that $\frac{\partial X}{\partial \mu} < 0$ for a wide range of random parameter values and it therefore follows that $\frac{\partial}{\partial \mu}\frac{\partial \alpha}{\partial \bar{\beta}} > 0$, see *main text* figure 3.2c. Similarly this holds for crowding, q.

From equation (A.7) it is clear that $\frac{\partial}{\partial b}\frac{\partial \alpha}{\partial \bar{\beta}} > 0$ when $\frac{\partial X}{\partial b} < 0$. Analysis indicates that $\frac{\partial X}{\partial b} < 0$ for a wide range of random parameter values and it therefore follows that $\frac{\partial}{\partial b}\frac{\partial \alpha}{\partial \bar{\beta}} > 0$, see *main text* figure 3.2b. Similarly this holds for recovery, γ.

Finally, since α is an increasing function of β, $\frac{\partial}{\partial b}\frac{\partial \alpha}{\partial \bar{\beta}} > 0$ implies that the trait value at the CSS will increase with an increase in b (this holds for all of the above parameters).

Appendix B

Parasite virulence in the non-seasonal DDV model cannot branch

For the trait to branch the singularity must be convergent stable (CS) and not evolutionarily stable (non-ES). The combination of these conditions results in the requirement

$$\left.\frac{\partial^2 r}{\partial\bar{\beta}\partial\beta}\right|_{\bar{\beta}=\beta=\beta^*} = \left.\left(\frac{\partial X}{\partial\beta} - c\bar{\alpha}'(\bar{\beta})\frac{\partial H}{\partial\beta}\right)\right|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{B.1}$$

$$\Leftrightarrow \qquad \left.\frac{\partial H}{\partial\beta}\frac{b+\gamma}{\beta(1+cH)}\right|_{\bar{\beta}=\beta=\beta^*} > 0 \tag{B.2}$$

where the invasion fitness, r, is given by equation (3.5) - *main text*. Equation (B.2) follows by combining the derivative of the equilibrium solution of equation (3.2) - *main text* with respect to β (i.e. $\frac{\partial}{\partial\beta}(\frac{1}{Y}\frac{dY}{dt}) = 0$), equation (B.1) and equation (3.6) - *main text*. Thus branching is only possible when

$$\frac{\partial H}{\partial\beta} > 0 \tag{B.3}$$

The derivatives of the endemic equilibria with respect to β are related according

to

$$\frac{\partial Y}{\partial \beta} = \frac{b+\mu}{b+\mu+\gamma}\frac{\beta - c\alpha}{c\alpha}\frac{\partial X}{\partial \beta} \tag{B.4}$$

$$\frac{\partial Z}{\partial \beta} = \frac{\gamma}{b+\mu+\gamma}\frac{\beta - c\alpha}{c\alpha}\frac{\partial X}{\partial \beta} \tag{B.5}$$

$$\frac{\partial H}{\partial \beta} = \frac{\beta}{c\alpha}\frac{\partial X}{\partial \beta} \tag{B.6}$$

where equation (B.6) follows from differentiating the equilibrium condition of equation (3.2) - *main text* with respect to β (i.e. $\frac{\partial}{\partial \beta}(\frac{1}{Y}\frac{dY}{dt}) = 0$) and equations (B.4) and (B.5) follow from combining equation (B.6), the equilibrium condition of equation (3.3) - *main text* and $\frac{\partial H}{\partial \beta} = \frac{\partial X}{\partial \beta} + \frac{\partial Y}{\partial \beta} + \frac{\partial Z}{\partial \beta}$. Hence, the derivatives $\frac{\partial X}{\partial \beta}, \frac{\partial Y}{\partial \beta}, \frac{\partial Z}{\partial \beta}, \frac{\partial H}{\partial \beta}$ are all sign-equivalent.

Differentiating the equilibrium condition of equation (3.1) - *main text* with respect to β (i.e. $\frac{\partial}{\partial \beta}(\frac{1}{X}\frac{dX}{dt}) = 0$) and substituting in equations (B.4-B.6) leads to

$$\frac{\partial X}{\partial \beta}\phi = XYc\alpha(b+\mu+\gamma) \tag{B.7}$$

where

$$\phi = ((a\beta(1-2qH) - c\alpha(b+Y\beta))(b+\mu+\gamma) + (\beta - c\alpha)(\mu\gamma - X\beta(b+\mu))) \tag{B.8}$$

The endemic equilibrium point (X, Y, Z) is stable only if the determinant of the Jacobian of the system given by equations (3.1-3.3) - *main text* at the endemic equilibrium is negative. It can be shown that this condition implies that

$$\phi < 0 \tag{B.9}$$

and hence it follows from equation (B.7) that $\frac{\partial X}{\partial \beta} < 0$ and thus $\frac{\partial H}{\partial \beta} < 0$ by equation (B.6). Since this contradicts the branching requirement given by equation (B.3) parasite virulence cannot branch under the assumptions of this model.

□

Appendix C

Branching in a related *DDV* model

We consider a related DDV model with an alternative representation of the virulence component

$$\frac{dX}{dt} = aH(1-qH) - bX - \beta XY + \mu Z \tag{C.1}$$

$$\frac{dY}{dt} = \beta XY - (\alpha_0 + \alpha_D H + b + \gamma)Y \tag{C.2}$$

$$\frac{dZ}{dt} = \gamma Y - (b+\mu)Z \tag{C.3}$$

Here virulence is separated into two components, an adaptive baseline component, $\alpha_0 = \alpha_0(\beta)$, that is present even when there is no density pressure and hence host condition is good, and a density dependent component α_D which is not adaptive with β. There is therefore one cost to being infected which varies with parasite load and another that varies with host condition but not pathogen load.

The invasion fitness is given by

$$r = \bar{\beta}X - (\bar{\alpha}_0(\bar{\beta}) + \alpha_D H + b + \gamma) \tag{C.4}$$

with $\bar{\beta}$ representing mutant transmission and the population equilibria taken for resident trait values. The singularity condition is given by

$$\left(\frac{\partial \bar{\alpha}_0}{\partial \bar{\beta}} - X\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} = 0 \tag{C.5}$$

For evolutionary branching to be possible, the the singularity must be convergent

stable, requiring

$$\left(\frac{\partial^2 r}{\partial \bar{\beta}^2} - \frac{\partial^2 r}{\partial \beta^2}\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} = \left(-\frac{\partial^2 \bar{\alpha}_0}{\partial \bar{\beta}^2} - \bar{\beta}\frac{\partial^2 X}{\partial \beta^2} + \alpha_D \frac{\partial^2 H}{\partial \beta^2}\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{C.6}$$

$$\Leftrightarrow \qquad \left(-\frac{\partial^2 \bar{\alpha}_0}{\partial \bar{\beta}^2} + 2\frac{\partial X^*}{\partial \beta}\right)\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{C.7}$$

where equation (C.7) follows by differentiating the equilibrium condition of equation (C.2) twice with respect to β (i.e. $\frac{\partial^2}{\partial \beta^2}(\frac{1}{Y}\frac{dY}{dt}) = 0$) and combining with equation C.6. Additionally for branching the singularity must not be ES, requiring

$$\frac{\partial^2 r}{\partial \bar{\beta}^2}\Bigg|_{\bar{\beta}=\beta=\beta^*} = -\frac{\partial^2 \bar{\alpha}_0}{\partial \bar{\beta}^2}\Bigg|_{\bar{\beta}=\beta=\beta^*} > 0 \tag{C.8}$$

$$\Leftrightarrow \frac{\partial^2 \bar{\alpha}_0}{\partial \bar{\beta}^2}\Bigg|_{\bar{\beta}=\beta=\beta^*} < 0 \tag{C.9}$$

therefore if $\frac{\partial X}{\partial \beta} < 0$, then the convergence stability requirement (C.7) can be satisfied when evolutionary stability is violated. This would require that the curvature of the trade-off be small relative to the rate of change of susceptible density with respect to transmission rate. Therefore, if $\frac{\partial X}{\partial \beta} < 0$, branching can occur for trade-offs with a declerating cost structure that are close to linear.

Differentiating and combining the equilibrium conditions of equations (C.1-C.3) with respect to β yields the same relations as equations (B.4-B.6) but this time with $c\alpha = \alpha_D$

$$\frac{\partial Y}{\partial \beta} = \frac{b+\mu}{b+\mu+\gamma}\frac{\beta-\alpha_D}{\alpha_D}\frac{\partial X}{\partial \beta} \tag{C.10}$$

$$\frac{\partial Z}{\partial \beta} = \frac{\gamma}{b+\mu+\gamma}\frac{\beta-\alpha_D}{\alpha_D}\frac{\partial X}{\partial \beta} \tag{C.11}$$

$$\frac{\partial H}{\partial \beta} = \frac{\beta}{\alpha_D}\frac{\partial X}{\partial \beta} \tag{C.12}$$

As per *Appendix B*, substitution of equations (C.10-C.12) into the equation given by differentiating the equilibrium condition of equation (C.1) with respect to β (i.e. $\frac{\partial}{\partial \beta}(\frac{1}{X}\frac{dX}{dt}) = 0$) yields

$$\frac{\partial X}{\partial \beta}\phi = XY\alpha_D(b+\mu+\gamma) \tag{C.13}$$

where

$$\phi = ((a\beta(1-2qH) - \alpha_D(b+Y\beta))(b+\mu+\gamma) + (\beta-\alpha_D)(\mu\gamma - X\beta(b+\mu))) \tag{C.14}$$

and the condition that the determinant of the Jacobian of the system given by equations (C.1-C.3) must be negative in order for the endemic equilibrium to be stable implies that

$$\phi < 0 \tag{C.15}$$

and hence it follows from equation (C.13) that $\frac{\partial X}{\partial \beta} < 0$ for this model.

Thus the convergence stability condition given by equation (C.7) can always be met, once the trade-off has the correct curvature, for this model when evolutionary stability is violated (i.e. when equation C.9 is satisfied). We have confirmed that branching occurs using simulations of the evolutionary process.

□

Appendix D

Proof that the CSS position is unaffected by seasonality in the basic *SIRS* model.

The basic *SIRS* model corresponds to equations (3.1-3.3) - *main text* when $c = 0$. When the dynamics are periodic the invasion fitness of the system over a period from P_0 to P_1 is:

$$r = \frac{1}{T}\int_{t=P_0}^{t=P_1} (\bar{\beta}X(t) - (\bar{\alpha}(\bar{\beta}) + b + \gamma))dt, \tag{D.1}$$

where $\bar{\beta}$ denotes the mutant transmission rate and X is the equilibrium susceptible density at the endemic steady state of the SIR system which depends on the resident trait β.

Integrating both sides of the infecteds ODE, equation (3.2) - *main text*, over the period from P_0 to P_1 gives

$$\int_{t=P_0}^{t=P_1} \frac{\dot{Y}(t)}{Y(t)}dt = \int_{t=P_0}^{t=P_1} (\beta X(t) - (\alpha + b + \gamma))dt \tag{D.2}$$

$$\Leftrightarrow [\ln Y(t)]_{t=P_0}^{t=P_1} = \int_{t=P_0}^{t=P_1} (\beta X(t) - (\alpha + b + \gamma))dt \tag{D.3}$$

and since $Y(P_1) = Y(P_0)$ the average susceptible density is conserved as follows

$$\frac{1}{T}\int_{t=P_0}^{t=P_1} Xdt = \frac{(\alpha + b + \gamma)}{\beta} \tag{D.4}$$

Substituting the above expression into the invasion fitness, equation (D.1), yields

$$r = \frac{\bar{\beta}}{\beta}(\alpha(\beta) + b + \gamma) - (\bar{\alpha}(\bar{\beta}) + b + \gamma) \tag{D.5}$$

Since this expression does not depend on the amplitude of seasonality, δ, (or either the forcing period, ϵ, or the period of the dynamics, T) the evolutionary steady state equation ($\frac{\partial r}{\partial \bar{\beta}}|_{\bar{\beta}=\beta=\beta^*} = 0$) will also be independent of δ (and ϵ, T). The CSS values (β^*,α^*), therefore, will not vary with the amplitude or period of seasonality. There is an analogous proof for the case of chaotic dynamics.

□

Appendix E

Models displaying invariance of evolutionary attractor under seasonality.

The property that evolved virulence is invariant under increased seasonality of forced parameters for a virulence transmission trade-off can be found for a variety of models and a variety of forced parameters.

In the basic *SIRS* model the parameters a, μ, q and β (and combinations of them) can be forced without altering the evolutionary end-point of virulence. We have shown that this is true for a in *Appendix D*. In the case of μ and q the argument is identical to *Appendix D* as neither parameter appears in the infecteds ODE (equation 3.2 - *main text*).
In the case of β, the invasion fitness again is equation (D.1) which now includes a time dependence in the β term. Averaging the infecteds equation yields

$$\int_{t=P_0}^{t=P_1} \beta X dt = T(\alpha + b + \gamma) \tag{E.1}$$

$$\Leftrightarrow \frac{1}{T}\int_{t=P_0}^{t=P_1} g(t) X dt = \frac{(\alpha + b + \gamma)}{\beta_0} \tag{E.2}$$

where the latter equation follows from the definition of forced transmission, $\beta = \beta_0 g(t)$. Substituting this equation (E.2) into the invasion fitness leads to

$$r = \frac{\bar{\beta}_0}{\beta_0}(\alpha(\beta) + b + \gamma) - (\bar{\alpha}(\bar{\beta}) + b + \gamma) \tag{E.3}$$

which is not dependent on the amplitude of forcing, δ, or on the period of the forcing, ϵ, or on the period of the dynamics, T. The remaining parameters, however, α, b and γ, result in a time dependent invasion fitness when they are forced.

Therefore, for *SIRS* type models, forcing of any parameter that does not govern the infectious period has no impact on the evolutionary endpoint of parasite virulence. The result, however, does not generally extend to models with an exposed class [198].

Chapter 4

Lifespan and immunity

4.1 Preface

The material in this chapter corresponds to the following 2013 publication,

Boots, M., R. Donnelly, and A. White, 2013. Optimal immune defence in the light of variation in lifespan. Parasite Immunology 35:331–338.

I was a joint author providing, in particular, the theoretical aspects of the study.

4.2 Introduction

Parasites and pathogens are ubiquitous and by definition harm the individuals that they infect. As a consequence, a wide range of constitutive and induced innate, as well as adaptive, defence mechanisms, ranging from behavioural avoidance and mechanical barriers to complex humoral and cellular immune systems, have evolved [109, 110]. However, these responses are far from uniform. There is considerable variation between individuals in their immune investment, and more broadly hosts respond very differently to their various diseases [109, 110]. This is perhaps particularly noticeable in terms of whether long lasting immune memory occurs to different diseases in vertebrates. Life-long immunity is far from the normal outcome of recovery with partial and/or waning immune memory found in response to many infectious diseases, such as syphilis, while no immune memory occurs to other infections, such as rota-viruses and many bacterial infections in humans [109, 110]. These outcomes may be considered as failures of the immune system, but the burgeoning ecological and evolutionary immunity research community is highlighting the importance of understanding both the level and the type of immune investment as an intrinsic outcome of the ecological and evolutionary interactions between the host and the infectious organism [109–111]. From this point of view we need to

understand the considerable variation in immune investment in the context of both the overall fitness of the host and the population level impacts of immunity. The ecological/epidemiological impacts of immunity are critical since they feedback into the evolution of host defence. In particular investment in immunity may reduce the prevalence of disease, thereby reducing the risk of infection and as a consequence the relative importance of investment in stronger immunity. As such infection risk is a result of the dynamics of the host-parasite interaction and it is the nature of these interactions that define the benefits of different immune strategies.

A key epidemiological driver of immune memory is the chance of future exposure to the same infection and as such host lifespan has been discussed as a key driver of immune investment within the evolution of life-history community [112–114]. Within this conceptual framework longer lived species should invest more in acquired immunity while shorter lived species should invest more in innate relative to acquired immunity [115]. There are a number of empirical studies in vertebrates that have looked for evidence of this pace of life hypothesis including meta-analyses [116, 117] and single studies with both non-specific [118–120] and specific challenges and/or immune measures [121–125]. The results are somewhat mixed, but when the more specific challenges or measures are used evidence for the pace of life hypothesis is often found [122–124]. While the acquired immune system of vertebrates is well studied, a traditional view is that vertebrates have evolved immune memory in part due to their relatively long lifespans. However, it is becoming increasingly apparent that in invertebrates previous exposure to parasites can also lead to increased protection on subsequent challenge [126–128]. Furthermore, there are many vertebrate and invertebrate host parasite interactions where long-lived hosts do not acquire long-lived immunity [109, 110]. Eco-evolutionary theory has been recently developed with a focus on understanding the impact of the interactions between individual life-history characteristics such as life-span and ecological dynamics on the evolutionarily optimal outcome. Here we review the insights of this theory on the implication of host lifespan to the evolution of immunity.

Fundamental to the idea that there is an optimal level of defence is that there are costs to defence. It is now clear that there may be costs through either the use of the defence mechanisms [129–134] or through the costs of their development and maintenance in the absence of infection [57, 135–137]. For example, the activation of the immune system following challenge with a pathogen has been shown to be costly [133, 138, 139] and much of the virulence of many diseases may be due to some form of such immuno-pathology [130, 134, 140]. However it is the costs of having a strong immune system in the absence of disease that is critical to determining the optimal level of defence. Such evolutionary constitutive costs to high immune defence have been demonstrated directly using selection experiments in a number

of systems [57, 135–137] and it is clear that the nature of these costs may depend on the host environment [141]. Constitutive costs may be manifested in other life-history traits such as slower development rates [57, 141] or decreased competitive ability [137] or through trade-offs between different components of defence [110]. When defence against infectious disease is costly, not only is there an optimal level of defence, but the level of immunity is a fundamental component of the life-history and fitness of the host. Such evolutionary costs may also help to generate and maintain the considerable variation in the level of defence within host populations seen in nature [19, 139, 142–144]. Eco-evolutionary theory has been developed to allow us to understand the factors that lead to different levels of investment in different forms of defence.

In addition to the importance of costs in the immune system, there are also likely to be important ecological feedbacks to the evolution of defence against infectious organisms. Ecological feedbacks result from the impact that changes in defence have on the epidemiology of the disease which then feedback to affect the evolution of defence. Intuitively, the degree of the defence invested in by hosts will affect the prevalence of the parasite in the population. Since this prevalence defines the risk that an individual will be challenged, it influences the selection pressure for defence. For example, consider a mutation that reduces the chance that an individual becomes infected in the first place, but this defence is costly such that it is traded-off against another component of the hosts life-history (for example higher defence results in a slower development time and therefore a lower rate of reproduction). If the benefits of this costly resistance in terms of a reduced risk of infection is relatively high, the cost is worth paying and the mutation will spread through the population. However, as the frequency of the resistance allele increases in the population, more individuals are resistant to infection leading to a lower prevalence of the infectious disease in the population. Since the prevalence is lower, there is less selective advantage for the resistant allele. This negative frequency-dependent selection results from the feedback between the ecological dynamics (the prevalence) and the evolutionary ones (the spread of costly resistance genes). Any defence mechanism that reduces the prevalence of the parasite (e.g. avoiding infection in the first place, recovering more rapidly from infection, or controlling the growth rate of the parasite within the host) leads to this form of feedback. Furthermore, since these defence mechanisms reduce the parasite's prevalence, they also reduce parasite fitness and are therefore classified as forms of resistance [47, 50, 145, 146]. In contrast, a defence mechanism that ameliorates the damage that a parasite causes its host, such that it reduces an individual's disease-induced mortality, will lengthen the infectious period of the parasite. As such this type of defence mechanism increases parasite prevalence as it spreads through the host population, leading to positive frequency dependence. This

form of defence is known in the evolutionary literature as tolerance [47, 50, 145, 146], and due to its different ecological feedback, it leads to very different evolutionary outcomes [19, 47, 50].

The contrasting ecological feedbacks between resistant and tolerant traits is a fairly intuitive example of the phenomenon. However as ecological scenarios become more complex with, for example, multiple infection, different transmission modes or long-lasting acquired immunity, the ecological feedbacks in turn become complex and less straightforward to understand intuitively. Formal theory, is then useful in order to make predictions on the impact of different biological mechanisms on the evolution of defence and to guide our understanding of the processes that underlie these predictions.

4.3 Theory

One of the main reasons for developing a mathematical model in order to understand the ecology or evolution of disease is that it clearly defines the processes that we are considering and the ones that we are not. Using these models we can define a number of different mechanisms of host defence from their impact on the epidemiology of the disease. Consider a general infectious disease model

$$\frac{dS}{dt} = aH - qH^2 - bS - \beta SI + (1-\nu)\gamma I + \delta R \tag{4.1}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + b + \gamma)I \tag{4.2}$$

$$\frac{dR}{dt} = \nu\gamma I - (b + \delta)R \tag{4.3}$$

that compartmentalises a host population into densities of susceptibles, S, infecteds, I, and immunes, R and where the dynamics of these densities and hence the total host density, given by $H = S + I + R$, are described by non-linear ordinary differential equations. All parameters are non-negative and $\nu \in [0, 1]$. Hosts produce susceptible offspring at rate a which is limited by intra-specific crowding, q, so that the carrying capacity is given by $K = (a - b)/q$. Hosts die at natural death rate b. Transmission of infections is a mass action process between susceptible and infected types, with transmission coefficient β and infected hosts suffer additional disease induced mortality (virulence) at rate α. Infected hosts recover at rate γ, and a proportion ν of these individuals become immune to the pathogen while the remaining individuals return to a susceptible state. Recovered hosts lose immunity at rate δ. This general model form can capture a wide range of classical infectious scenarios.

For example if $\nu = 0$ (or $\delta = \infty$) the model represents a Susceptible-Infected-Susceptible (SIS) framework, where there is no immune memory and recovered individuals are completely susceptible to the disease, while if $\delta = 0$, we have the Susceptible-Infected-Removed (SIR) model with lifelong immunity.

The model can be used to investigate a number of different classes of defence based on their epidemiological impacts. The fundamental forms of host defence can be defined as follows: (i) avoidance reduces the probability of becoming infected and resistant hosts therefore have a lower transmission rate (β), (ii) recovery increases the rate of clearance (γ), whereas (iii) tolerance reduces virulence (α). Finally, acquired immunity evolves as either (iv) a higher probability of acquiring immunity (ν), or (v) a lower rate of loss of immunity (δ).

The costs associated with defence can be due to trade-offs with other defence mechanisms or through other determinants of fitness in the host. Trade-offs within the immune system can be examined by correlations within defence traits such that, for example, high avoidance results in lower recovery . However, there is relatively little theory on optimal levels of defence given trade-offs between different immune components [150], with most of the work focused on constitutive costs manifested in other components of the host life-history [19, 68, 147–151]. Generally the costs are assumed to be manifested in the rate of reproduction, a, which includes both the number of offspring produced and the rate of maturation. As such there are a wide range of mechanisms that may underpin these costs.

The theoretical approach of evolutionary invasion analysis is useful when we want to examine evolutionary dynamics in response to ecological feedbacks. We now outline the mathematical details of this approach in the context of the evolution of acquired immunity. It is assumed that traits are continuous and that the level of immunity is determined due to the action of many alleles at many loci. This type of modelling is therefore less appropriate when there are major genes that encode for large immune responses. When we use mathematical analysis to predict the outcome we also assume that evolution proceeds through rare mutations of small effect. However, the robustness of the predictions of the theory to a relaxation of this assumption can be examined through simulation. In the analysis we vary parameters such as host lifespan and predict the optimal investment in different types of immunity, for example avoidance and recovery, given different ecological scenarios. For this reason it is an appropriate theoretical framework in which to address our question of how host lifespan should impact on optimal investment in defence.

4.3.1 The adaptive dynamics of acquired immunity

We define two models. Firstly, model 1 explores the evolution of probability of clearance to immunity (ν) with an assumption of reproductive costs to investment in resistance, i.e. $\nu = f(a)$ with $d\nu/da < 0$. For simplicity we consider SIR dynamics so that immunity is lifelong, i.e. $\delta = 0$.

In model 2 we explore the evolution of waning immunity (δ) with an assumption of reproductive costs to investment in resistance, i.e. $\delta = g(a)$ with $d\delta/da > 0$. For simplicity we assume that recovery from infection always leads to immunity, i.e. SIRS dynamics with $\nu = 1$.

A criteria for a successful mutant invasion of a resident population is that the average change in the mutant population per invader is positive

$$\theta = \rho_S T_S + \rho_I T_I + \rho_R T_R > 0 \tag{4.4}$$

where ρ_i is the per capita growth rate of mutant hosts (i.e. hosts with trait ν_m (a_m) in model 1 and δ_m (a_m) in model 2), when an individual mutant, whose epidemiological state is given by i, invades a population consisting solely of individuals with the resident trait. The invasion criteria given by equation 4.4 is a proxy for invasion fitness when it involves only growth rates from an invader who has entered class i for the first time [156]. The proxy can be used to assess evolutionary behaviour in both model 1 and model 2 (see the later *Appendix I* for a justification of the use of this condition as a proxy for invasion fitness).

Applying the methods of adaptive dynamics [31, 32], which assumes monomorphic trait distributions and small mutations, the evolutionary dynamics of model 1 and 2 can be analysed. This approach assesses properties of the fitness of a new mutant strain attempting to invade a resident population at its dynamic attractor.

From the invasion fitness it is possible to determine the position (located at the zeros of the fitness gradient) and nature of evolutionary singularities. A singularity which is both convergence stable (CS, i.e. the population evolves towards the singularity), and evolutionary stable (ES, i.e. a population in the vicinity of the singularity cannot be invaded) is known as a continuously stable singular strategy (CSS, Eshel [152]).

In this study we consider only trade-offs with a suitable (accelerating) cost structure to ensure that the singularity is a CSS. We examine how the position of the CSS, and hence the level of optimal immunity, varies with model parameters.

Using the approach outlined above for the evolution of immunity, Miller et al. [153] investigated the evolution of resistance traits in the general model of host parasite dynamics given by equations 4.1-4.3. They showed that longer-lived individuals

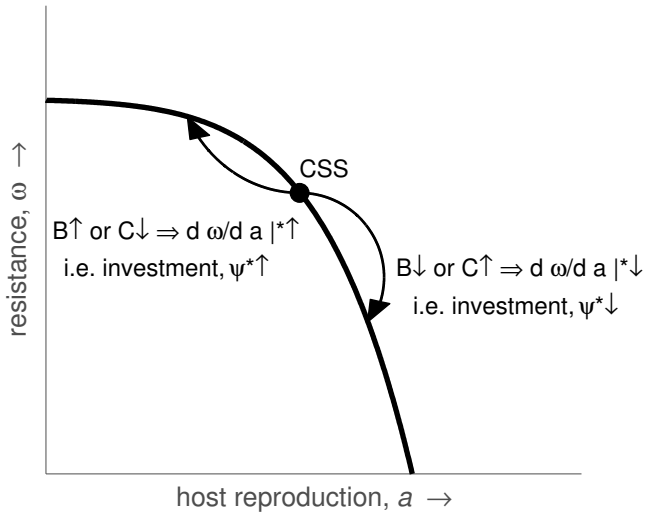

Figure 4.1: *Geometric explanation of the cost benefit analysis of host immunity.* The trade-off between host reproduction, a, and probability of clearance to immunity, ν.

relying only on innate immunity to defend against parasites do generally invest more in immunity since increased lifespan often leads to higher disease prevalence. The first take home message of this paper and indeed a number of other theoretical papers whose focus was not just on the impact of host lifespan [19, 68, 147–151] is that longer-lived hosts should invest more in innate immunity. It is interesting to reflect on this result in the context of the generally held idea that immune memory is selected for in longer-lived hosts. The theory tells us that longer lifespans promote more immune investment in organisms that only have innate immunity.

Once the host has the potential for immune memory, the relationship between investment in immunity and lifespan becomes much more complicated. Firstly once there is immune memory investment in the components of innate immunity no longer necessarily increases with lifespan. When there is long-lived acquired immunity, investment in avoidance tends to increase with lifespan initially, but in very long lived hosts, investment may fall to low levels (Fig 2A,D in Miller et al. [153] and in Fig 5 of the earlier paper of van Boven and Weissing [154] that examined some of the same questions in a different framework). A similar pattern can be observed for both recovery and tolerance (see Miller et al. [153] Fig $3B, D$, although for some parameter combinations investment increases with lifespan see Miller et al. [153] Fig $3A$,C and van Boven and Weissing [154] Fig $3, 4$). These results can be understood due to the effects of immune individuals on the prevalence of the disease: immune individuals may lead to lower prevalence and therefore less investment in other components of the immune system. It must also be borne in mind that long-lived individuals bear the costs of higher investment in immunity over their relatively longer lifespan.

Perhaps the key results of the Miller et al. [153] paper were found when they

considered the investment in immune memory itself. In the case of acquired immunity there are two traits that can be considered as measures of the investment in immunity. The first of these is the propensity to acquire immune memory in the first place. A second trait is how long immune memory lasts before individuals revert to susceptibility. Miller et al. [153] showed that there is a distinction between the effects of lifespan on optimal immune investment in acquired immunity measured in these two ways. For clarity we repeat and extend the analysis of Miller et al. [153] here (Fig 4.2). Investment in the rate of waning immunity always increases with host lifespan (Fig 4.2c). As such immune memory is predicted to last longer in longer lived organisms. However, optimal investment in the probability of clearance to immunity is maximal for an intermediate lifespan (Fig 4.2a). This is a critical result since it shows that investment in acquiring immunity in the first place is not selected for by longer lifespans. We now develop some more general theory in order to highlight how epidemiological feedbacks drive this result.

4.3.2 Density dependence and the optimal probability of acquiring immunity

Evolutionary invasion analysis of the probability of acquiring immunity in the SIR model (i.e. equations 4.1-4.3 with $\delta = 0$, $\nu = \nu(a)$) indicates that the trait will evolve in the direction of the fitness gradient until

$$\frac{\partial \nu(a^*)}{\partial a} = -\frac{1}{L\alpha\gamma}\left(\frac{I^*}{H^*}\right)^{-2} \tag{4.5}$$

where a^* denotes reproductive rate on the evolutionary attractor and $L = 1/b$ is a measure of host lifespan. We assume costly immunity ($\nu(a)$ is a decreasing function of a) and accelerating costs (in order to ensure the singularity is a CSS). See appendix F for more details.

Equation 4.5 identifies the singular strategy by giving the value of the slope of the tangent to the trade-off curve at the singularity, Figure 4.1. It is composed of a term that depends directly on lifespan and a term that depends on equilibrium prevalence (the term in brackets, I/H) which can indirectly depend on lifespan. Equation 4.5 implies that high equilibrium prevalence selects for high acquired immunity, ν. Also, in the absence of the ecological feedback (i.e. holding prevalence constant so that only the lifespan term varies) longer lifespan selects for increased immunity. The effect of increasing host lifespan is a balance of these selective pressures (i.e. the selective pressure through the lifespan term and the selective pressure through the prevalence term), resulting in increasing optimal immunity when the selective pres-

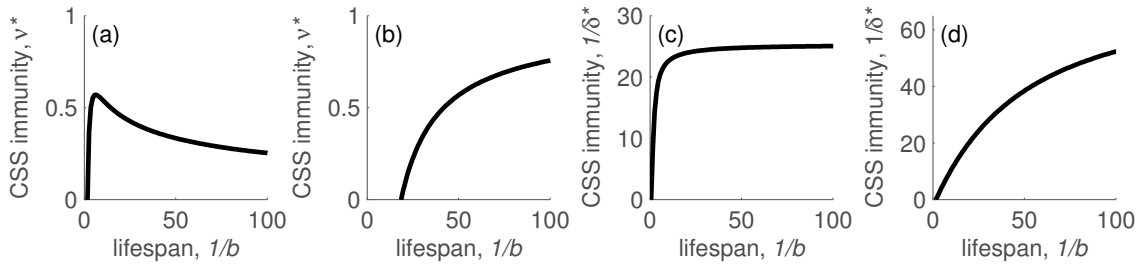

Figure 4.2: *Optimal investment in immunity against lifespan under different assumptions of density dependence in the hosts.* In (a) and (b), evolution of the probability of acquiring immunity, $\nu*$ against host lifespan where in (a), regulation of host population occurs through host self-regulation ($q = 0.02$), and in (b), where there is no density dependence in the host and regulation only occurs through the pathogen ($q = 0$). In (c) and (d), evolution of waning immunity, $\delta*$ against host lifespan where in (c), regulation of host population occurs through host self-regulation ($q = 0.02$), and in (d), there is no density dependent self-regulation in the host ($q = 0$). The figures presented in (a) and (c) are reproductions of Miller et al. (50) using alternative tradeoffs and parameter values. The trade-off and parameter values for evolution of the probability of acquiring immunity, $\nu*$, were $\nu = 1 - a^4/2^4$ and $\alpha = 5, c = 1, b = 1$ in (a) and $\nu = 1 - a^4/1^4$ and $\alpha = 10, c = 0.15, b = 1$ in (b). The trade-off and parameter values for evolution of waning immunity, $\delta*$, were $1/\delta = 100 - 100a^4/2^4$ and $\alpha = 5, c = 1, b = 1$ in (c) and $1/\delta = 100 - 100a^4/1^4$ and $\alpha = 10, c = 0.15, b = 1$ in (d).

sures are in agreement ($\partial/\partial L(I^*/H^*) > 0$) and potential for decreasing immunity with lifespan when the selective pressures are in opposition ($\partial/\partial L(I^*/H^*) < 0$). Therefore, a necessary (but not sufficient) condition for decreasing immunity with increasing lifespan is

$$\frac{\partial}{\partial L}\frac{I^*}{H^*} = \frac{\partial a^*}{\partial L} - q\frac{\partial H^*}{\partial L} + \frac{1}{L^2} < 0 \tag{4.6}$$

where prevalence at equilibrium is given by equation 4. When $q = 0$ equation 4.6 can only hold when $\partial a^*/\partial L < 0$ and hence investment in immunity always increases with lifespan. Since total host density increases with increasing host lifespan the term $q\frac{\partial H^*}{\partial L}$ in equation 4.6 contributes to a decrease in prevalence but only when $q > 0$. Therefore, once intra-specific crowding limits host reproduction prevalence can decrease with lifespan leading to a selective pressure for decreasing immunity.

Miller et al. [153] assumed that there was density dependence in the host population such that it is self-regulating ($q > 0$ in equations 4.1-4.3) and discussed that this may be critical to their key result that optimal probability of acquiring immunity, ν^*, is maximal for an intermediate lifespan when immunity is permanent, see figure 4.2a. van Boven and Weissing [154] also speculated on the importance of such density dependence and stated that determining the evolution of immunity when

the host is not self regulated is an open question. Here we examine this question in detail and use models to explain the processes that underpin the results. When there is no density dependence in the host population ($q = 0$ in equations 4.1-4.3) it can be shown analytically that the optimal probability of acquiring immunity, ν^*, always increases with lifespan, see figure 4.2b. Therefore, the additional population feedback generated by intra-specific crowding has a significant qualitative impact on how the optimal probability of acquiring immunity varies with lifespan.

Biologically, increasing lifespan results in an increasing total host density. When $q > 0$ this brings the system closer to carrying capacity and hence reduces net births which in turn lowers equilibrium prevalence given by

$$\frac{I}{H} = \frac{(a - qH - b)}{\alpha} \tag{4.7}$$

The lower prevalence that results selects for decreased acquired immunity. But there is always a further selective pressure for increased immunity due to the increased exposure to infection that longer lifespan entails. When lifespan is sufficiently large the former pressure dominates the latter. Thus, investment in the probability of acquiring immunity is increasing for lower lifespans and decreasing for higher lifespans, see figure 4.2a. When $q = 0$ and the host population is regulated by the infection the prevalence no longer decreases with increasing host density and therefore optimal immunity can only increase with host lifespan, see figure 4.2b.

When it is the length of immunity that evolves (the rate of waning immunity, δ^*) against host reproduction optimal investment has a similar form to equation 4.5. Here too total host density increases with lifespan leading to a decrease in prevalence when $q > 0$. However, in this model, exposure to the infection increases more rapidly with increasing lifespan because this time immunity is not permanent. Thus, the selection for increased immunity is far stronger in this model. This effect dominates the selective pressure for decreasing investment from the prevalence feedback and hence optimal investment in immunity increases with lifespan, see figure 4.2*c*. The results presented here (and in van Boven and Weissing [154] and Miller et al. [153]) show that investment in immunity has a complex relationship with lifespan. In particular, density-dependent demography that limits the host turnover and therefore impacts on prevalence can lead to a reduction in investment in immunity as host lifespan increases.

4.4 Parasite 'lifespan'

Clearly therefore the lifespan of the host can have a major impact on optimal immune defence, but what can we say about the lifespan of the parasite? The lifespan of macro-parasitic worms are likely to have an impact on the optimal level of immunity but there is however very little theoretical work that considers the impact of macroparasites on optimal immune investment. In one sense however the lifespan of microparasites (pathogens such as viruses, bacteria etc) can be considered to be the infectious period, which is determined by a combination of the recovery rate and the host death rate due to infection (virulence). Clearly these two parameters are influenced by both the host and the parasite, but a useful simplification is that the recovery rate is a host trait while virulence can be defined as a parasite trait [155]. From this point of view acute parasites with a short lifespan have a high virulence while chronic long-lived parasites have a low virulence. Generally the highest level of immunity will be invested against parasites with intermediate virulence [19, 147]. In this sense parasites of intermediate lifespan promote the highest investment in immunity in their hosts. This is intuitively straightforward to understand. Chronic parasites causing low virulence are relatively harmless to individuals and therefore there is less selection for costly immunity. Highly pathogenic acute parasites are dangerous to individuals, but the prevalence of the disease in the population reduces at higher virulence (due to their short infectious period). Generally, therefore, low virulence results in a high risk of challenge with disease but a low impact infection while high virulence has a high individual impact on fitness but there is a relatively low risk of challenge. As such intermediate virulence leads to the greatest combination of risk of exposure and fitness reduction and therefore the highest investment in costly immunity. From this perspective parasites of intermediate life-span promote the highest investment in immunity.

4.5 Discussion

The existing models have therefore given us some important insights into the impact of host and parasite lifespan on investment in immunity. Like all models they are wrong. The models make simplifying assumptions and by definition look at particular epidemiological processes. This is the key strength of simple models: they make the assumptions we are making in our arguments on optimal immune investment explicit. As discussed previously it has been classically assumed that longer-lived organisms should be selected to invest in long-lived immune memory. The explicit theory that we have discussed has shown that the outcome is more nuanced and in many situations immune memory is optimised at intermediate lifespans. How-

ever, the classical verbal arguments may implicitly assume a number of different mechanisms while the theory that we have reviewed makes very general explicit assumptions. In particular the current theory assumes that hosts are faced with an endemic disease. If in contrast organisms are faced with recurring epidemics, the impact of being a longer-lived host and therefore being subject to repeated epidemics are potentially considerable. The theory should therefore be extended to examine the impact of epidemic pathogens. Furthermore the theory has made the assumption that hosts are faced with one genetically identical infectious disease agent. Clearly a longer-lived organism faced with multiple pathogens or multiple strains of the same pathogen is more likely to face the same pathogen/strain multiply than a short-lived organism. It is therefore important to examine theoretically the impact of longevity on investment in immune defence in the face multiple and/or diverse pathogens. These are just two of a number of possible important extensions of the theory that would help us to gain a better understanding of the role of host lifespan on the optimal level of immune investment. Furthermore, the burgeoning empirical literature on the impact of life-span on immune function [117–120, 122–124] is creating an exciting opportunity to link the theory more directly to empirical results, driving both the theory and experimental tests of the theory. The current work emphasises that it is important to develop explicit theory in the face of potentially complex ecological feedbacks that define optimal immunity.

Appendix F

Evolutionary invasion analysis of the probability of acquiring immunity

In evolutionary invasion analysis we evaluate the resident population at its dynamic equilibrium (i.e. $H^r > 0$) while in contrast the mutant population is so rare it has no impact on the dynamics (i.e. $H^m = 0$). Equations 4.1-4.3 can be extended to encompass both resident and mutant sub-populations. The ODEs for the mutant strain differs to equations 4.1-4.3 in two respects. Infection occurs upon contact with both resident and mutant infecteds (i.e. $\beta^m(I^r + I^m)$) and host birth rate is reduced by a factor depending on total host density (i.e. $qH^m(H^r + H^m)$). Summing the ODEs for the mutant strain results in an ODE for total mutant density

$$\frac{dH^m}{dt} = S^m(a - qH^r - b) + I^m(a - qH^r - b - \alpha) + R^m(a - qH^r - b) \tag{F.1}$$

When a rare mutant is susceptible, its contribution to the growth of the overall mutant population is given by the part of the first term in equation F.1 that is in parantheses. We denote this by ρ_S. Similarly, the contribution from a rare infected mutant is ρ_I and from a rare immune mutant is ρ_R,

$$\rho_S = a^m - qH^r - b \tag{F.2}$$

$$\rho_I = a^m - qH^r - b - \alpha \tag{F.3}$$

$$\rho_R = a^m - qH^r - b \tag{F.4}$$

A mutant host will be born susceptible and will either die susceptible or become

infected. Infected individuals may either die in that state or recover. In model 1 they may recover to permanent immunity where they will die or they may recover back to a susceptible state. Ignoring repeated visits the average time a mutant host is susceptible, denoted T_S, is the inverse of the rates at which individuals leave the mutant susceptible class i.e. $T_S = 1/(b + \beta^m I^r)$, note that I^m is assumed to be so small that it does not affect dynamics. The average time a mutant host is infected, denoted T_I, is the probability the susceptible mutant becomes infected multiplied by the average time the infected host remains infected i.e. $T_I = [\beta^m I^r/(b + \beta^m I^r)] \times [1/(\alpha + b + \gamma)]$. The average time a mutant host is immune, denoted T_R, is the probability the susceptible mutant becomes infected multiplied by the probability the infected host recovers to immunity multiplied by the average time the immune host remains immune i.e. $T_R = [\beta^m I^r/(b + \beta^m I^r)] \times [\nu^m \gamma/(\alpha + b + \gamma)] \times [1/b]$,

$$T_S = 1/(b + \beta I^r) \tag{F.5}$$

$$T_I = \beta I^r/((b + \beta I^r)(\alpha + b + \gamma)) \tag{F.6}$$

$$T_R = \beta I^r \nu^m \gamma/((b + \beta I^r)(\alpha + b + \gamma)b) \tag{F.7}$$

Following [156], a proxy for invasion fitness is

$$\theta = T_S \rho_S + T_I \rho_I + T_R \rho_R \tag{F.8}$$

with T_S, T_I and T_R from equations F.5-F.7 and ρ_S, ρ_I and ρ_R from equations F.2-F.4.

For simplicity, repeated visits to the epidemiological states were not included in the T_S, T_I and T_R terms. The proxy ignoring repeated visits is equivalent to the proxy with repeated visits since the geometric series arising from repeated visits is common to the T_S, T_I and T_R terms and can therefore be factored out.

Solving the singularity equation given by

$$\frac{\partial \theta}{\partial a^m} = 0 \tag{F.9}$$

for the invasion fitness given by F.8 results in equation 4.5.

Chapter 5

The epidemiological feedbacks critical to the evolution of host immunity

5.1 Preface

The material in this chapter corresponds to a manuscript which is currently under review at *Evolution*,

Donnelly, R., White, A. and Boots, M., 2014 The epidemiological feedbacks critical to the evolution of host immunity, *under review*.

I am the lead author in this forthcoming work.

5.2 Introduction

It is recognised that during evolution changes in the dominant genotypes within a population (and therefore phenotypes) will alter the ecological dynamics. New ecological dynamics in turn alter selection pressures dictating the new genotypes and phenotypes that can spread and fixate. Using an ecologically explicit approach to modelling evolution it is possible to identify the relationship between optimal investment and its ecological determinants and thereby distill complex feedbacks into a simpler combination of selection pressures. In this study we use the example of host resistance to highlight these feedbacks by systematically comparing how ecology feeds back to optimal investment for different combinations of host and parasite interactions.

There is substantial variation in host defence and this is likely to reflect the wide range of interactions between hosts and parasites. For example, parasites can

damage their hosts by causing a loss of fertility or increasing mortality and hosts may differ in their capacity for immune memory. In general, any mechanism that offsets fitness loss due to infection is a form of host defence. Despite the immunological complexity of defence, functionally it is achieved through just a few routes [110, 156]. 'Tolerance' mechanisms reduce the damage that infection causes while on the other hand, resistance mechanisms including avoidance, recovery and acquired immunity directly counter the parasite [153]. Genes conferring resistance, since they reduce parasite fitness, in addition to increasing host fitness, cause the prevalence of infection, a dynamic ecological variable, to decline and so reduce the advantage of resistance [19, 49, 157, 158]. On the other hand, genes conferring tolerance may cause prevalence to rise, if they lengthen the infectious period, increasing the advantage of tolerance as it spreads through the population [50, 159]. In other words, resistance causes negative frequency dependence through an ecological feedback which can prevent fixation while tolerance causes positive frequency dependence which leads to fixation. This is a clear and relatively intuitive instance of the central role that ecological feedbacks play in the evolution of immune defence. Beyond this, however, there are likely to be more complicated and subtle ecological feedbacks that help define the evolutionary dynamics of the immune system.

Approaches to modelling evolution by natural selection differ in their treatment of explicit ecology and genetics [29, 30, 160–163]. In evolutionary invasion analysis [31, 32] density-dependent ecological dynamics are explicitly modelled with feedbacks to fitness but at the expense of genetic detail. The framework assumes a separation of ecological and evolutionary time scales as well as rare mutations of small effect with quantitative continuous phenotypes. The advantage of these simplifying assumptions is that density and frequency dependent selection emerge naturally from these eco-evolutionary models and this has proved effective in understanding how population level processes determine evolutionary outcomes. The assumption of quantitative continuous phenotypes is also a good one for the majority of immune mechanisms that are characteristically associated with quantitative trait loci (for example, cytokine activation in Dupuis et al. [164], porcine leukocyte regulation in Edfors-Lilja et al. [165] and rodent Th1 development in Gorham et al. [166]).

There is a large body of theoretical research focused on the evolution of resistance in the context of ecological feedbacks. In early work based on competition between two strains that differ in their level of resistance, Antonovics and Thrall [157] and Bowers et al [49] demonstrated that negative frequency dependence supports coexistence of resistance types. Boots and Haraguchi [19] developed this for continuous, quantitative resistance and showed that decelerating costs to resistance could lead to dimorphism or to maximum or minimum resistance levels but accelerating costs lead to single optimal phenotypes. Understanding the patterns of

optimal investment in host defence for different host-parasite systems is a key challenge. For example, van Boven and Weissing [154] and Miller et al. [153] both showed that optimal investment in resistance in hosts with permanent immune memory can be low for long-lived species. Boots et al. [167] demonstrate that this is due to low prevalence as a result of low population turnover at high lifespans. However, there are many counter-intuitive patterns in optimal resistance [153] and it remains unclear how ecological feedbacks determine these outcomes. For instance, the key dynamic feedback to resistance has been identified as force of infection in van Baalen [155] and van Baalen [168] and Boots and Haraguchi [19] yet disease prevalence is emphasised in Miller et al. [153]. Beyond the simple descriptive case that qualitatively contrasts tolerance and resistance, eco-evolutionary feedbacks can be complex and therefore understanding the key determinants of optimal resistance remains an important challenge. Here, by considering different host-parasite interactions we develop theory linking subtle differences in ecological context to fundamentally different patterns in optimal resistance. The significance of our findings extend beyond host parasite systems and emphasise that uncovering complex feedbacks is key to understanding the biological processes that underpin evolutionary behaviour.

5.3 Methods

5.3.1 Epidemiological Model

Following the methods of Anderson and May [169], we consider a system of non-linear ordinary differential equations that compartmentalises total host population density, H into susceptible, S, infected, I and immune/recovered, R, densities

$$\frac{dS}{dt} = a(S + \mu I + R) - q(S + \mu I + R)H - bS - \beta SI + (1 - \nu)\gamma I + \delta R \tag{5.1}$$

$$\frac{dI}{dt} = \beta SI - (\alpha + b + \gamma)I \tag{5.2}$$

$$\frac{dR}{dt} = \nu\gamma I - (b + \delta)R \tag{5.3}$$

All parameters are non-negative and $\mu,\ \nu\ \in [0, 1]$. Hosts produce susceptible offspring at rate a which is limited by intra-specific crowding, q, so that the carrying capacity in the absence of disease is given by $K = (a - b)/q$. Pathogens alter the fecundity of infected hosts such that hosts do not reproduce while infected when $\mu = 0$ or there is no effect on host reproduction when $\mu = 1$. Hosts die at natural death rate b. Transmission of infecteds is a mass action process between susceptible

and infected types, with transmission coefficient β. Infected hosts suffer additional disease induced mortality (virulence) at rate α. Infected hosts recover at rate γ, and a proportion of these recoveries, ν, acquire immunity to the pathogen which wanes at rate δ, while the remaining individuals return to a susceptible state.

This model captures several infection scenarios of interest. If $\nu = 0$ the model represents a Susceptible−Infected−Susceptible (SIS) framework, where there is no immune memory and recovered individuals are completely susceptible to the infection. On the other hand if $\nu = 1$ and $\delta = 0$ it represents a Susceptible−Infected−Recovered (SIR) model with life-long immunity (or $SIRS$ with waning immunity if $\delta > 0$). Host resistance can be achieved through the following routes. Avoidance, which decreases the rate of transmission (β). Recovery, which increases the rate of clearance of infection (γ). Finally, acquired immunity, which either increases the probability of inducing acquired immunity (ν) or increases the expected duration of acquired immunity ($1/(b+\delta)$) [153].

5.3.2 Evolutionary Model

The association of resistance with physiological costs through the development and maintenance of resistance capability has a firm empirical basis [57, 136, 137, 170]. Following these studies we assume that costs are paid through decreased host fecundity (i.e. we make avoidance, recovery and acquired immunity decreasing functions of host reproduction rate).

In evolutionary invasion analysis [31, 32], invasion fitness, Θ, is the asymptotic growth rate of a mutant population introduced at low density into an environment set by a resident population at equilibrium, i.e.

$$\Theta_r(m) = \frac{1}{H^m}\frac{dH^m}{dt}\bigg|_{H^r>0, H^m=0} \tag{5.4}$$

In equation 5.4 r and m denote resident and mutant, and we are evaluating the resident population at its dynamic equilibrium (i.e. $H^r > 0$) while in contrast the mutant population is so rare it has no impact on the dynamics (i.e. $H^m = 0$). Equations 5.1-5.3 can be extended to encompass both resident and mutant subpopulations. The ODEs for the mutant strain differs to equations 5.1-5.3 in two respects. Infection occurs upon contact with both resident and mutant infecteds (i.e. $\beta^m(I^r + I^m)$) and host birth rate is reduced by a factor depending on total host density (i.e. $q(S^m + \mu I^m + R^m)(H^r + H^m)$). The rate of change of the mutant host population, dH^m/dt, is then the sum of the mutant equations, i.e.

$$\frac{dH^m}{dt} = S^m(a - qH^{tot} - b) + I^m(\mu(a - qH^{tot}) - b - \alpha) + R^m(a - qH^{tot} - b)\Big|_{H^r>0, H^m=0} \tag{5.5}$$

where $H^{tot} = H^r + H^m$. The expressions in parentheses in equation 5.5 are the per capita growth rates of the mutant host population when the rare mutants are in the respective classes, denoted σ_S^m, σ_I^m and σ_R^m. Invasion fitness can therefore be written

$$\Theta_r(m) = p_S^m \sigma_S^m + p_I^m \sigma_I^m + p_R^m \sigma_R^m \Big|_{H^r>0, H^m=0} \tag{5.6}$$

where p_S^m is the proportion of mutant hosts who are susceptible (i.e. $p_S^m = S^m/H^m$ and similarly for p_I^m and p_R^m). Substituting the relation $p_S^m = 1 - p_I^m - p_R^m$ into equation 5.6 and noticing in equation 5.5 that $\sigma_S^m = \sigma_R^m$ leads to

$$\Theta_r(m) = \sigma_S^m - p_I^m((1-\mu)(a - qH^r) + \alpha)\Big|_{H^r>0, H^m=0} \tag{5.7}$$

Since the first term in equation 5.7 is equivalent to the fitness of uninfected hosts, the second term provides an exact expression for the fitness loss due to infection. It is equal to the product of prevalence in the mutant population and harm caused by infection, henceforth denoted D i.e.

$$D = (1-\mu)(a - qH^r) + \alpha \tag{5.8}$$

This shows that infection can be fought with two distinct strategies that offset fitness loss, $p_I^m D$. Resistance reduces prevalence, p_I^m, on the other hand, tolerance reduces damage D (by alleviating either disease induced mortality or loss of fertility).

We introduce a trait, ω, that is useful in the analysis, determining the phenotypic value of quantitative resistance (i.e. $\omega = f(a)$). The host population evolves in the direction of the mutant gradient of invasion fitness until it reaches an evolutionary singularity. There, by definition, the fitness gradient is zero so that singularities, a^*, satisfy

$$\left.\frac{\partial \Theta}{\partial a^m}\right|_* = 0 \tag{5.9}$$

where the vertical bar indicates that the expression is evaluated at the evolutionary equilibrium where resident equals mutant (i.e. $r = m = *$). A singularity, a^*, is evolutionary stable (ES) if $\partial^2\Theta/\partial a^{m2} < 0$ and convergence stable (CS) if $\partial^2\Theta/\partial a^{r2} - \partial^2\Theta/\partial a^{m2} > 0$. A singularity that is both ES and CS is uninvadable as well as attracting in an evolutionary sense (i.e. a Continuously Stable Strategy, CSS, [152] - an end point of evolution). In this study we analyse the dependence of optimal investment in resistance on the underlying ecological model for a range of model formulations. Our results are based on the assumption of diminishing returns for a host investing in resistance, i.e. a continuous trade-off between resistance and reproduction of any shape provided that reproduction is a decreasing function of resistance and that costs accelerate. When the parasite causes a loss of fertility, optimal investment in resistance with accelerating costs is a CSS [171], and hence an end-point of evolution. When the parasite has no effect on fertility, optimal investment in resistance with accelerating costs is a CSS when costs are sufficiently strongly accelerating [60, 61]. The results presented in this study assume a trade-off that makes the singularity studied a CSS (i.e. figures 5.1-5.4 are generated from trade-offs with strongly accelerating cost structures), however, the analysis outlined in this work applies more generally for any trade-off with an accelerating cost structure (but note that once the singularity is reached branching can occur if costs accelerate only weakly).

Solving equation 5.9 for the invasion fitness given by equation 5.7 and rearranging indicates that evolutionary singularities satisfy

$$\left.\frac{d\omega^m}{da^m}\right|_* = \left.\frac{(p_S + \mu p_I + p_R) - D\frac{\partial p_I^m}{\partial a^m}}{D\frac{\partial p_I^m}{\partial \omega^m}}\right|_* \tag{5.10}$$

$$= \left. -\frac{C}{B}\right|_* \tag{5.11}$$

where the numerator in equation 5.10 represents net cost and is therefore denoted by C, i.e. C represents the change in fitness induced by a reduction in reproduction that follows from an increased investment in resistance. Since $\partial p_I^m/\partial \omega^m < 0$, i.e. prevalence is a decreasing function of resistance, the denominator in equation 5.11 represents minus benefit and is denoted $-B$, i.e. B represents the change in fitness

induced by an increased resistance capability.

Equation 5.10 gives the position on the resistance-reproduction trade-off which corresponds to a singularity. As a consequence of costs rising with increasing investment with diminishing returns, any increase in the right hand side of equation 5.11 results in the location of the singularity shifting to low values of mutant reproduction. This corresponds to high investment in resistance, see figure $G1$ in *appendix* G. This implies that singular resistance is a cost benefit analysis so that optimal investment in resistance, ψ^*, is high whenever the benefit is large relative to the cost

$$\psi^* \propto \left.\frac{B}{C}\right|_* \tag{5.12}$$

The exact expression for host fitness is key to explaining the role of costs and benefits. However, the terms p_S^m and p_I^m that appear in cost and benefit (see equation 5.10) in practice are too complex to calculate.

A proxy for invasion fitness is a fitness criterion that shares the same singularities and evolutionary behavior. Following the biologically inspired proxy of Bowers and Turner [172] we replace the proportion of mutants who are infected, p_I^m, with the proportion of the expected lifespan a mutant spends infected, $\tilde{p}_I^m = T_I/T_H$, and similarly $\tilde{p}_S^m$ for p_S^m. The proxy replacements, $\tilde{p}_S^m$ and $\tilde{p}_I^m$ allow optimal investment in resistance to be expressed solely in terms of state variables and parameters of the epidemiological model. See appendix I for an explanation of why this replacement produces a proxy for invasion fitness.

Example: avoidance resistance. To provide a concrete example of how we determine the feedback on investment we consider in detail the evolution of avoidance in a host population. For simplicity we assume that the host has no ability to recover from infection ($\gamma = 0$) and that an infected host does not reproduce ($\mu = 0$).

A mutant host will be born susceptible and will either die susceptible or become infected. Infected individuals remain in that state until death. The average time a mutant host is susceptible, denoted T_S, is the inverse of the rates at which individuals leave the mutant susceptible class i.e. $T_S = 1/(b + \beta^m(I^m + I^r))$, see equation 6.1. The average time a mutant host is infected, denoted T_I, is the probability the susceptible mutant becomes infected multiplied by the average time the infected host remains infected i.e. $T_I = [\beta^m I^r/(b + \beta^m I^r)] \times [1/(\alpha + b)]$, see equation 5.2.

From the expressions for T_S and T_I we find proxy terms for prevalence and susceptible frequency

$$\tilde{p}_S^m = \frac{T_S}{T_S + T_I} = \frac{\alpha + b}{\alpha + b + \beta^m I^r} \tag{5.13}$$

$$\tilde{p}_I^m = \frac{T_I}{T_S + T_I} = \frac{\beta^m I^r}{\alpha + b + \beta^m I^r} \tag{5.14}$$

Differentiating the proxy for prevalence, equation 5.14, with respect to resistance (in this case transmission, β), and using equation 5.13 leads to

$$\frac{\partial \tilde{p}_I^m}{\partial \beta^m} = \frac{1}{\beta^m} \tilde{p}_S^m \tilde{p}_I^m \tag{5.15}$$

Therefore, substituting equation 5.15 into the expression for the benefit of resistance in equation 5.11 and using the definition of D in equation 5.8, the benefit for this model evaluated at the singularity is

$$B = \frac{(a - qH + \alpha)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{5.16}$$

where for simplicity we have dropped the mutant symbol, m, from the mutant frequency expressions. The equilibrium condition for equation 5.1 with $\gamma = 0$ and $\mu = 0$ is $a - qH = b + \beta I$, so that benefit can be further simplified to

$$B = \frac{(\alpha + b + \beta^* I)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{5.17}$$

$$= \frac{(\beta^* S + \beta^* I)}{\beta^*} \tilde{p}_I \tilde{p}_S \tag{5.18}$$

$$= I \tilde{p}_S \tag{5.19}$$

where equation 5.18 follows from equation 5.17 because of the equilibrium condition from equation 5.2, i.e. $\alpha + b = \beta S$. Futhermore, equation 5.19 follows from 5.18 since $S + I = H$ in the numerator of 5.18 and this cancels with H in the denominator of p_I. On the other hand recalling the definition of cost from equation 5.11, the cost evaluated at the singularity is

$$C = \tilde{p}_S \tag{5.20}$$

since $\mu = 0$ and since $\tilde{p}_I^m$ is independent of a (see equation 5.14). Finally, since optimal investment in resistance is a cost benefit analysis

$$\psi^* \propto \frac{B}{C} = I \tag{5.21}$$

Equation 5.21 indicates that optimal investment in avoidance is proportional to the density of infecteds. As long as costs increase with resistance such that diminishing returns apply then the relationship depends on the exact form of the trade-off in a quantitative sense only, it has no qualitative impact on the pattern of optimal investment with respect to life-history.

5.4 Results

Following the procedure outlined in the previous section we present expressions in table 1 for optimal investment in resistance for various host-parasite frameworks and the main routes to resistance (more detail on deriving the expressions is provided in *appendix H*). Table 5.1 indicates that optimal investment for each resistance model is proportional to a simple function of a single key dynamic feedback. This leads to clear qualitative patterns for each model. This is supported by plots of optimal investment against the dynamic feedback, see figures 5.1-5.4 *i*). We additionally show how optimal investment varies with life-history in figures 5.1-5.4 *ii*) (for host lifespan, $1/b$), and figures 5.1-5.4 *iii*) (for host crowding, q). The closed circles and diamonds represent results of ODE-solving simulations of the adaptive dynamics process throughout (and the simulation results are in agreement with our analytical findings, see Boots et al. [68] for more information on the simulation procedure).

We first consider pathogens that both prevent host reproduction when infected (i.e. $\mu = 0$) and increase mortality ($\alpha > 0$). Since previous model studies have often not considered loss of fertility when infected we limit these results to innate resistance in hosts lacking immune memory (i.e. $\nu = 0$). When the parasite prevents host fertility, optimal investment is proportional to equilibrium infecteds density, I, scaled by case mortality, $(\alpha + b)/(\alpha + b + \gamma)$, see table 5.1 $A2$ and figure 5.1 (b) i). Both the cost and benefit of resistance vary with life-history parameters, see equation 5.10, and therefore the expressions in $A1$ and $A2$ of table 5.1 reflect an interaction of cost and benefit.

When the parasite has no effect on fertility, the dynamic feedback is disease prevalence for all forms of resistance, see table 5.1 $B1$-$B4$. In particular, when resistance is innate (through either recovery or avoidance) in a host lacking immune memory, investment is always greatest at intermediate prevalence, see table 5.1 $B1$ SIS and $B2$ SIS and figure 5.2 (a) i) and (b) i). Here, when prevalence is low

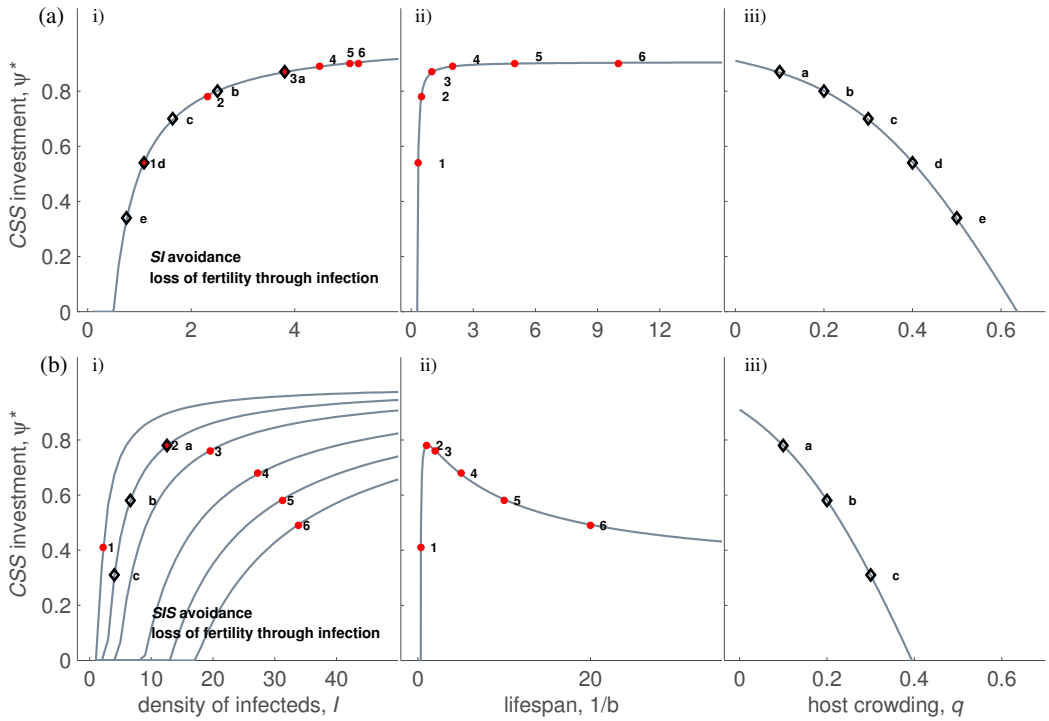

Figure 5.1: *CSS investment in innate resistance to an infection associated with loss of fertility.* In (a) there is no recovery from infection i.e. $\gamma = 0$. In (b) there is recovery from infection $\gamma = 5$. In both (a) $i)$ and (b) $i)$ shows the dependence of investment on the density of infecteds, I, while $ii)$ and $iii)$ throughout show the variation in investment as lifespan and crowding change. Closed circles and diamonds in each figure represent the final level of evolved resistance from ODE simulations of the evolutionary process. The resistance-reproduction trade-off was $\omega(a) = (1 - exp(-Q * (amax - a)))/(1 - exp(-Q * (amax - amin)))$ with $Q = 5$, $amax = 5$, $amax = 3$ for $\beta = \beta_0(1 - 0.4\omega(a))$. Parameters were: $\mu = 0$ $\beta_0 = 1$ in (a) and (b) and $\alpha = 4$ in (a) and $\alpha = 0.1$ in (b). CSS investment relies on case mortality which is always 1 when $\gamma = 0$ but depends on natural mortality when $\gamma > 0$ leading to curves for different values of natural mortality in (b) $i)$. The value of b for each curve corresponds to the location of the red simulation marker in (b) $ii)$, i.e. 1 corresponds to $L = 0.5$, 2 to $L = 1$, 3 to $L = 2$, 4 to $L = 5$, 5 to $L = 10$ and 6 to $L = 20$ where lifespan, L, equals $1/b$.

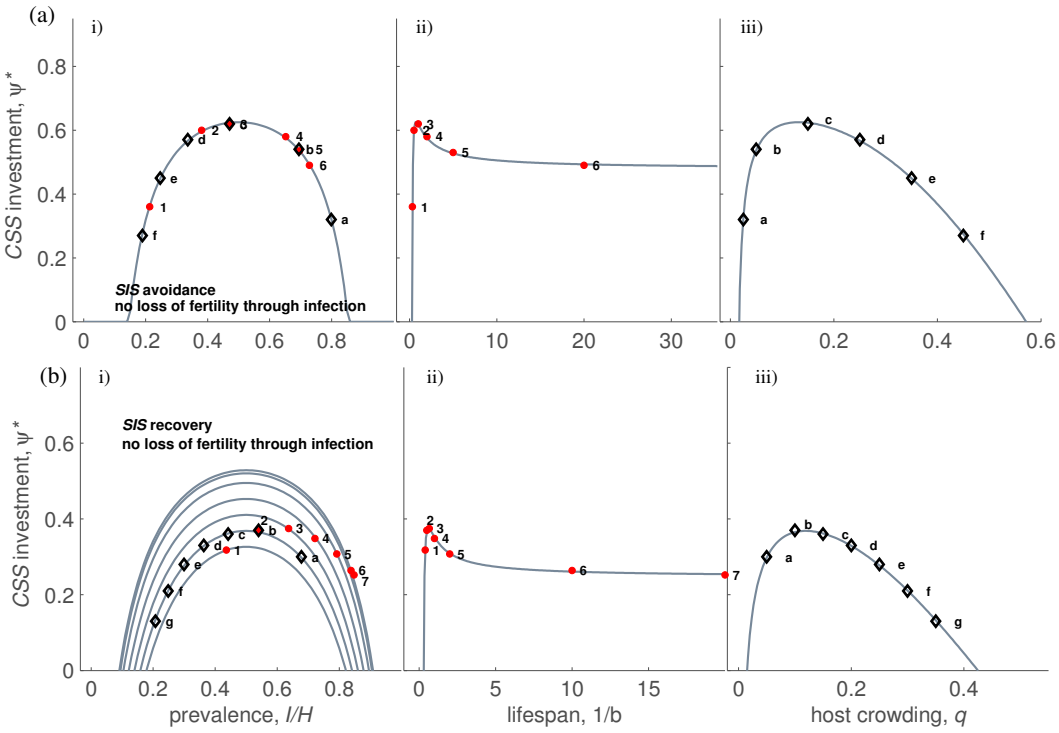

Figure 5.2: *CSS investment in innate resistance to an infection that has no impact on host fertility where the host has no capacity for immune memory i.e. SIS population.* In (a) the resistance is through avoidance while in (b) it is through recovery. In both (a) $i)$ and (b) $i)$ we show the dependence of investment on disease prevalence, I/H, while $ii)$ and $iii)$ throughout show the variation in investment as lifespan and crowding changes. Closed circles and diamonds in each figure represent the final level of evolved resistance from ODE simulations of the evolutionary process. See caption of figure 5.1 for the trade-off, $\omega(a)$ which affects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$ and affects recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$. In both (a) and (b) $\mu = 1$. In (a): $\beta_0 = 1$, $\alpha = 4$, $\gamma = 0.1$ and $b = 1$. In (b): $\alpha = 3$, $\gamma_0 = 2.5$ and $b = 2$. In the case of recovery *CSS* investment is in the length of the infectious period which depends on natural mortality leading to curves for different values of natural mortality in (b) $i)$. The value of b for each curve corresponds to the location of the red simulation marker in (b) $ii)$, i.e. 1 corresponds to $L = 1/4$, 2 to $L = 1/2$, 3 to $L = 1/1.5$, 4 to $L = 1$, 5 to $L = 2.5$, 6 to $L = 10$ and 7 to $L = 20$ where lifespan, L, equals $1/b$.

	SIS	SIR	$SIRS$
	$\nu = 0$	$\nu = 1$	B3 $\nu(a)$ & $\delta = 0$
			or B4 $\delta(a)$ & $\nu = 1$
avoidance *infertile infecteds*			
A1 no recovery	$\psi^* \propto I$	–	–
A2 with recovery	$\psi^* \propto \frac{\alpha+b}{\alpha+b+\gamma} I$	–	–
all forms *fertile infecteds*			
B1 avoidance	$\psi^* \propto \alpha \frac{I}{H}\left(1 - \frac{I}{H}\right)$	$\psi^* \propto \alpha \frac{I}{H}(1 - (\frac{b+\gamma}{b})\frac{I}{H})$	–
B2 recovery	$\psi^* \propto \alpha \frac{I}{H}\left(1 - \frac{I}{H}\right)$	$\psi^* \propto \alpha \frac{I}{H}\left(\frac{\alpha I}{bH} + 1\right)$	–
B3 acquired immunity (prob.)	–	–	$\psi^* \propto \frac{\alpha\gamma}{b}\left(\frac{I}{H}\right)^2$
B4 acquired immunity (length)	–	–	$\psi^* \propto \alpha\gamma\left(\frac{I}{H}\right)^2$

Table 5.1: Proportional expressions for optimal investment in resistance, ψ^*. In the case of evolving recovery, ψ^* represents investment in the inverse of the infectious period (i.e. $(\alpha + b + \gamma)^{-1}$) and hence recovery. In the case of evolving acquired immunity through the waning immunity rate, ψ^* represents investment in the duration of immunity (i.e. $b + \delta$) and hence acquired immunity. Column 1 corresponds to host populations without immune memory and therefore $\nu = 0$ for $A1$-$B4$ column 1. Column 2 corresponds to host populations with immune memory and for simplicity immunity is life-long and therefore $\nu = 1$ and $\delta = 0$. Our methods, see *appendix H*, require that there is no more than one route back to a susceptible state (i.e. $\delta > 0$ and $0 < \nu < 1$ cannot be true simultaneously) and therefore $\nu = 1$ with $\delta > 0$ in $B4$ column 3 and $\delta = 0$ with $\nu > 0$ in $B3$ column 3.

few transmission events are occurring and enhancement to avoidance or recovery has little impact on prevalence. When prevalence is high, the likelihood of the transmission of infection is high for susceptible individuals so that it is relatively futile to maintain or return individuals to a susceptible state. Therefore there is little benefit to increased innate resistance when prevalence is either low or high and this lies at the heart of the humpbacked dependence of investment on prevalence. Furthermore, when the parasite does not alter fertility, the direct cost of fitness is 1, see equation 5.10 (i.e. it does not depend on model details such as life-history values). Therefore the humpbacked relationship in table 5.1 $B1$ SIS and $B2$ SIS reflects only variation in the benefit of innate resistance. The strongly contrasting relationships seen between table 5.1 $A2$ (i.e. innate resistance with loss of fertility)

and table 5.1 $B1$ and $B2$ (i.e. innate resistance without loss of fertility) are a consequence of costs also varying with life-history when the parasite reduces host fertility (where cost depends on the proportion of mutants who are susceptible, as it is only they who pay the cost - infecteds do not reproduce).

When acquired immunity evolves to counter pathogens that have no effect on fertility investment is always higher for high prevalence, see table 5.1 $B3$ and $B4$. Optimal investment is qualitatively the same whether resistance is through probability of acquiring immunity or through duration of acquired immunity, see figure 5.3 (c) $i)$ and 5.4 (c) $i)$ for illustration. Since the parasite has no effect on fertility direct cost does not vary with model parameters. However, benefit now reflects an increase in proportion of immunes rather than an increase in proportion of susceptibles (amounting to a reduction in prevalence in both cases). As long as prevalence is not low it is always beneficial to boost immunity and this is particularly true when prevalence is high.

In the absence of immune memory, optimal investment in the two modes of innate resistance is qualitatively the same. However, with immune memory, investment patterns in avoidance and recovery are markedly different, compare figure 5.3 (b) $i)$ and 5.4 (b) $i)$ with figure 5.3 (a) $i)$ and 5.4 (a) $i)$. This is because the benefit of recovery and avoidance is similar in an SIS population since they both increase the susceptible frequency at the expense of infecteds frequency. However, in an SIR or $SIRS$ population, recovery mainly boosts immune frequency relative to prevalence while avoidance mainly boosts susceptible frequency. The parameter ν, mediates between these two outlets (i.e. for low ν optimal recovery resembles avoidance, for high ν it resembles acquired immunity).

The question of how optimal investment varies with life-history is entwined with how it varies with the dynamic feedback. In some cases optimal investment features a density independent coefficient term involving parameters from the host or parasite life-history, as, for example, with the density independent case mortality coefficient in table 5.1 $A2$. Intra-host crowding, q, which acts to reduce host births (or equivalently reduces juvenile survival), however, does not appear directly in any of the expressions in table 5.1. It can be shown that prevalence and infected density have a monotonic dependency on crowding (i.e. $\partial I/\partial q < 0$ and $\partial(I/H)/\partial q < 0$, results not included). Therefore, the variation in optimal investment due to variation in crowding mimics the relationship between optimal investment and the dynamic feedback (though the trend will be opposite since the dynamic feedback decreases with crowding). The result is that optimal investment has a humpbacked dependence on crowding when resistance is innate in an SIS population or when it is innate through avoidance in an $SIRS$ population, see figure 5.2 (a) $iii)$, 5.2 (b) $iii)$, 5.3 (a) $iii)$ and 5.4 (a) $iii)$. Investment decreases with increasing crowding when infect-

eds do not reproduce or when resistance is through acquired immunity or through recovery in an $SIRS$ population, see figure 5.1 A *iii*), 5.1 (*b*) *iii*), 5.3 (*b*) *iii*), 5.3 (*c*) *iii*), 5.4 (*b*) *iii*) and 5.2 (*c*) *iii*).

Wherever optimal investment depends on the natural mortality parameter through a coefficient term and not just through its implicit role in the dynamic feedback, there are distinct curves depending on the level of natural mortality, see figure 5.1 (*b*) *i*), 5.2 (*b*) *i*), 5.3 (*b*) *i*) − (*c*) *i*) and 5.4 (*b*) *i*) − (*c*) *i*). As natural mortality changes, and hence host lifespan changes, a conflict may arise between the directions of change of the coefficient term and the dynamic feedback term. This is one reason for maximal investment at intermediate lifespan, see figure 5.1 (*b*) *ii*), 5.3 (*b*) *ii*) and 5.3 (*c*) *ii*). Another reason is the natural hump-backed relationship between optimal investment and the population feedback, see figure 5.2 (*a*) *ii*), 5.2 (*b*) *ii*) and 5.3 (*a*) *ii*). Yet another reason requires life-long immunity, for then prevalence can be low at high lifespans (as immunes dominate the population), see figure 5.3 (*b*) *ii*) and 5.3 (*c*) *ii*). Of course maximal investment can occur for a combination of these reasons, see figure 5.3 (*a*) *ii*).

5.5 Discussion

It is clear that evolutionary change impacts population dynamics and that this in turn alters selection pressures. Such ecological feedbacks are particularly clear in host-parasite interactions where it is recognised that host resistance will impact on parasite prevalence, and that prevalence impacts the selection for resistance [19, 49, 50, 157, 158]. However, we have shown that the ecological feedback to optimal investment in immunity is nuanced and that its link to prevalence depends on the epidemiological scenario. In fact, optimal investment depends on the details of both the form of the evolving immunity (for example, innate versus acquired) and the nature of the disease (for example, the presence or absence of harmful effects on host fertility) as well as the details of host immunology (for example, host capacity for immune memory when it is innate immunity that is evolving). We have used a new analysis focused on the details of how selection for different types of immunity are determined by ecological feedbacks. One of our key results emphasises this subtlety since we show that when an infection causes a loss of fertility optimal investment in resistance varies with force of infection (i.e. the rate at which susceptibles are infected) whereas when infection only causes increased death rate investment instead varies with disease prevalence (i.e. the frequency of infected individuals in the host population). Critically though, and at first sight counter-intuitively, investment does not always increase with prevalence: the outcome depends on the epidemiology of the disease and the mode of resistance. Our detailed analysis has

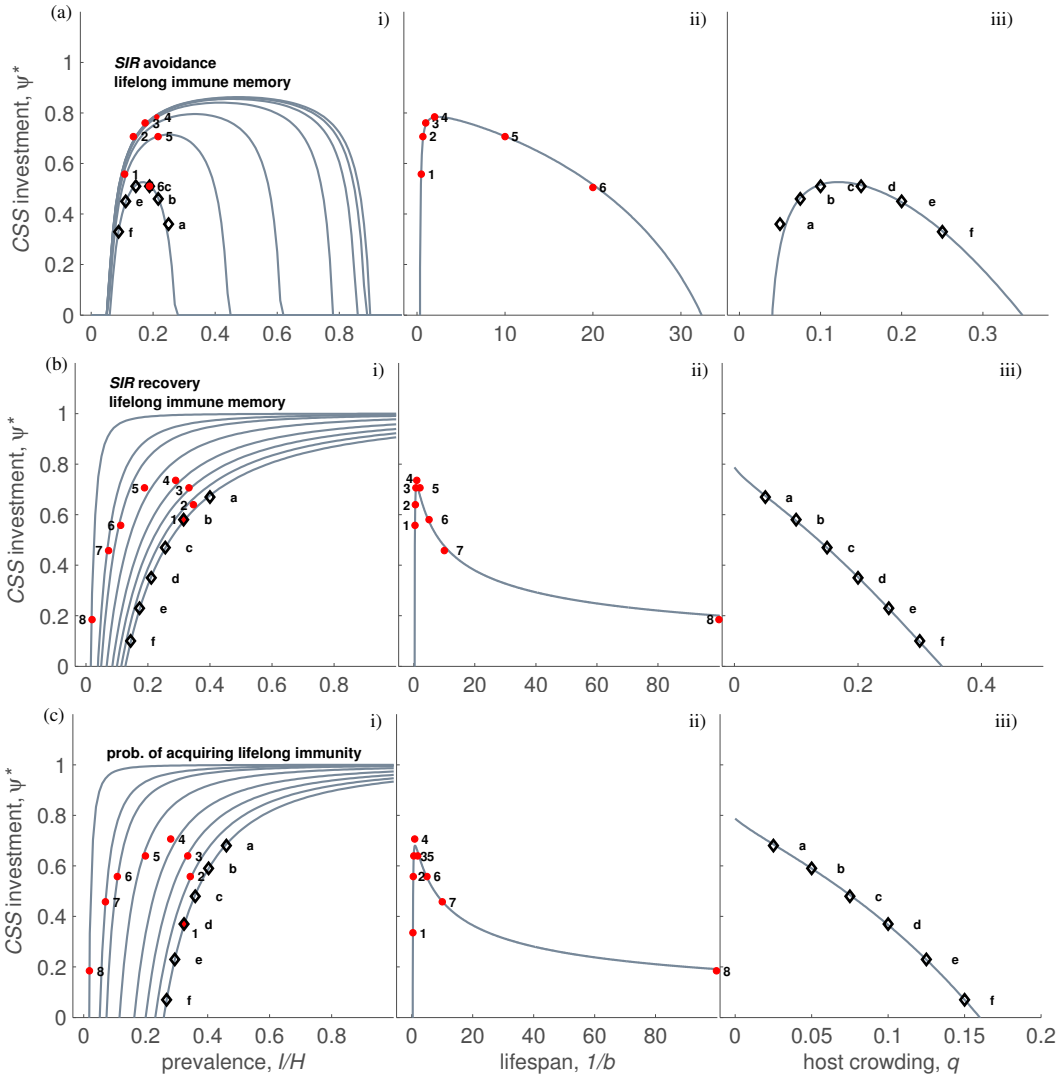

Figure 5.3: *CSS investment in resistance to an infection that has no impact on host fertility where the host possesses life-long immune memory i.e. SIR population except in* (c) *which is SIRS (in the sense that an SIR or SIS route is taken depending on* ν*) since recovereds return to a susceptible state with a probability that is evolving.* In panel (a), resistance is through avoidance, in (b) through recovery, and in (c) through the probability of acquiring immunity. See caption of figure 1 for the trade-off, $\omega(a)$ which effects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$, recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$ and the probability of recovering to immunity in (c) according to $\nu = \nu_0(1 + \omega(a))$. In (a), (b) and (c): $\mu = 1$. In (a): $\beta_0 = 1$, $\alpha = 10$ and $\gamma = 0.1$, $\nu = 1$, $q = 0.1$, $b = 0.05$. In (b) $\alpha = 3$, $\gamma_0 = 2.5$, $\nu = 1$, $q = 0.1$ and $b = 2.5$. In (c): $\alpha = 3$, $\gamma = 2.5$, $\nu_0 = 1$, $q = 0.1$, and $b = 2.5$. *CSS* investment relies directly on natural mortality when avoidance or recovery evolves in a host population containing immune individuals or when acquired immunity evolves. This leads to curves for different values of natural mortality in figure (a) *i*), (b) *i*), and (c) *i*). The value of b for each curve corresponds to the location of the red simulation marker in figure (a) *ii*), i.e. 1 corresponds to $L = 1/2$, 2 to $L = 1/1.5$, 3 to $L = 1$, 4 to $L = 2$, 5 to $L = 10$ and 6 to $L = 20$. In (b) *ii*) and (c) *ii*) the red markers also correspond to values of lifespan i.e. 1 corresponds to $L = 1/4$, 2 to $L = 1/2$, 3 to $L = 1/1.5$, 4 to $L = 1$, 5 to $L = 2.5$, 6 to $L = 5$, 7 to $L = 10$ and 8 to $L = 100$ where lifespan, L, equals $1/b$. Closed circles and diamonds in each figure represent the final level of resistance from ODE simulations of the evolutionary process.

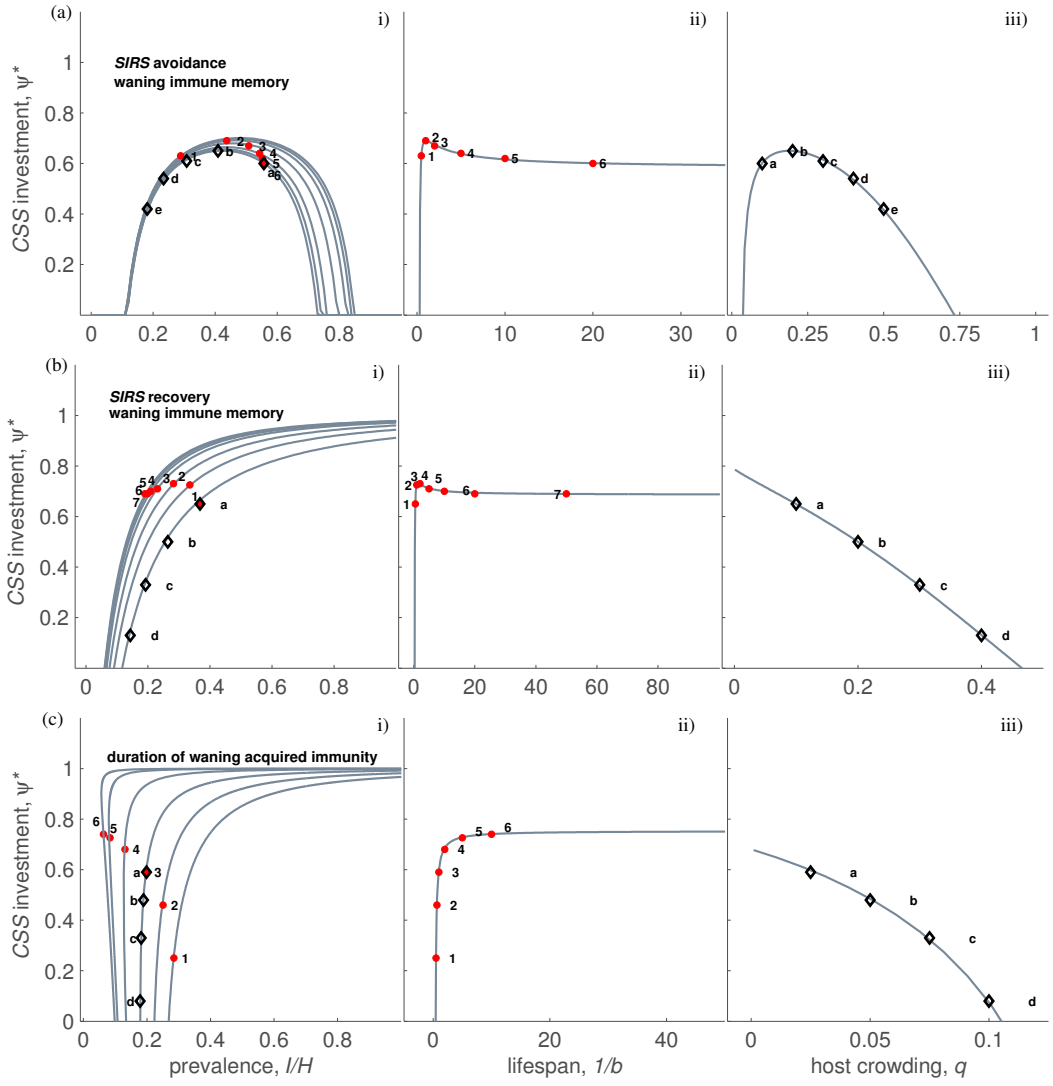

Figure 5.4: *CSS investment in resistance to an infection that has no impact on host fertility where the host possesses waning immune memory i.e. SIRS population.* In panel (a) resistance is through avoidance, in (b) through recovery, and in (c) through duration of acquired immunity. Note that while waning immunity is by necessity variable in (c) it is fixed in (a) and (b) (i.e. $\delta = 0.5$) and $\nu = 1$ throughout. See caption of figure 1 for the trade-off, $\omega(a)$, which effects transmission in (a) according to $\beta = \beta_0(1 - 0.4\omega(a))$, recovery in (b) according to $\gamma = \gamma_0(1 + \omega(a))$ and waning immunity in (c) according to $\delta = \delta_0(1 - \omega(a))$. In (a), (b) and (c): $\mu = 1$. In a: $\beta_0 = 1$, $\alpha = 5$, $\gamma = 5$, $\nu = 1$, $q = 0.1$ and $b = 0.05$. In (b): $\alpha = 3$, $\gamma_0 = 2.5$, $\nu = 1$, $q = 0.1$ and $b = 2$. In (c): $\alpha = 5$, $\gamma = 5$, $\nu = 1$, $q = 0.025$, $\delta_0 =$ and $b = 1$. *CSS* investment relies directly on natural mortality when avoidance or recovery evolves in a host population containing immune individuals or when acquired immunity evolves. This leads to curves for different values of natural mortality in figure (a) $i)$, (b) $i)$, and (c) $i)$. The value of b for each curve corresponds to the location of the red simulation marker in figure (a) $ii)$, i.e. 1 corresponds to $L = 1/2$, 2 to $L = 1$, 3 to $L = 2$, 4 to $L = 5$, 5 to $L = 10$ and 6 to $L = 20$. In (b) $ii)$ the red markers also correspond to values of lifespan i.e. 1 corresponds to $L = 1/2$, 2 to $L = 1$, 3 to $L = 2$, 4 to $L = 5$, 5 to $L = 10$, 6 to $L = 20$ and 7 to $L = 50$ and in (c) $ii)$ 1 corresponds to $L = 1/2$, 2 to $L = 1/1.5$, 3 to $L = 1$, 4 to $L = 2$, 5 to $L = 5$ and 6 to $L = 10$ where lifespan, L, equals $1/b$. Closed circles and diamonds in each figure represent the final level of resistance from ODE simulations of the evolutionary process.

allowed us to understand the nuanced impact of prevalence. In cases where infection has no effect on fertility, investment in innate resistance (i.e. avoidance or recovery in an SIS model or avoidance in an SIR model) is highest at intermediate prevalence while investment in immune memory (i.e. recovery in an SIR model or the duration of immunity as well as the probability of clearance to immunity in SIR and SIRS models) always increases with prevalence. Moreover, the presence of long lasting immune memory has a markedly different effect on two forms of innate resistance: avoidance and recovery. In the case of avoidance, it narrows the range of prevalence for which non-zero investment is optimal but does not qualitatively change the relationship between investment and prevalence. On the other hand, dependence of optimal investment in recovery on prevalence shifts dramatically so that investment always increases with prevalence when all recovereds become immune. More generally our work emphasises the importance of ecological feedbacks to evolutionary outcomes. Furthermore, it shows that key feedbacks depend on the ecological interaction between host and parasite so that simple intuition does not suffice. We now discuss in detail the subtle causes of these results and we outline the implications of our work.

A key insight from our models is that the impact of the parasite on host fecundity can have a major impact on the way in which the epidemiology feeds back into the evolutionary process. Specifically, optimal investment in immunity is a cost-benefit analysis in host fitness. The cost is proportional to the fraction of hosts who experience the loss of fecundity associated with costly resistance. When infected individuals reproduce normally all individuals experience the costs of resistance equally but when only susceptibles experience the cost (i.e. infected individuals do not reproduce) the cost is proportional to the frequency of susceptibles. Therefore, when infection effects fertility the cost depends on how the characteristics of both the host and parasite determine the ecology of the system. The relative frequency of susceptibles and infecteds will always matter to some extent if there is any impact of infection on host fecundity. Crucially, therefore, when infecteds reproduce normally, optimal investment reflects only variation in the benefits of resistance. When innate resistance evolves, the humpbacked relationship between optimal investment and prevalence that arises in this case reflects a humpbacked relationship between the benefit of resistance and prevalence. Furthermore, patterns of investment in innate resistance are the same whether the route is through avoidance or recovery. Here the benefit of resistance is the reduction in prevalence weighted by the damage from infection (when infecteds reproduce normally damage equals disease induced mortality, i.e. virulence). Innate resistance through recovery or avoidance achieves only a very slight reduction in prevalence, and hence has little benefit, if prevalence is already low or high. If prevalence is low, few transmissions occur because there

are relatively few infecteds, therefore neither avoidance nor recovery has a big effect on prevalence. If prevalence is high, returning individuals to a susceptible state (i.e. recovery) or maintaining them in a susceptible state (i.e. avoidance) only serves to feed the flames of future transmission and therefore has little effect on prevalence. This is an effect that has been noted in van Baalen [155], where it is in relation to the force of infection in a model with no reproduction of infecteds or density-dependence in host demography (van Baalen [155] describe this as a "give-up-hope effect" and point out a corresponding effect in optimal anti-predator traits in Abrams [173]). Therefore, though at first sight a hump-backed relationship between optimal investment and prevalence appears counter intuitive, in fact it is a hallmark of the evolutionary dynamics of innate resistance. In contrast, the positive association between optimal investment and the abundance of infecteds that we see when infecteds do not reproduce is the result of a more complex interplay of costs and benefits.

The more complex cost benefit relationship of investment in immunity when infection causes a loss of fertility has received less attention. When we look at the evolution of avoidance, we find that optimal investment is a simple increasing function of the abundance of infecteds. This result echoes that of Boots and Bowers [156] whose model features a parasite causing a loss of fertility and SI dynamics without recovery that are analogous to a predator−prey system. However a key factor that distinguishes between predator−prey and disease interactions is the possibility of recovery from an infected state to a susceptible state. At first sight the inclusion of recovery (i.e. SIS dynamics) might be thought to lead to dynamics that are more like the case where infection has no impact on fertility (since recovering infecteds are functionally similar to new-borns/juveniles coming from infected adults). However this is not the case. In fact the more general pattern is that optimal investment is proportional to the abundance of infecteds weighted by case mortality. When the rate of recovery is zero, infected individuals never recover and case mortality is one. Comparing this result for the case where infecteds do not reproduce with the results where infecteds do reproduce fully, reveals that qualitatively distinct patterns of optimal resistance result from assumptions of how infection impacts fertility. When infecteds do not reproduce, the simple increasing relationship between optimal investment and the abundance of infecteds that we find belies the complexity of the selection pressures involved. Once again, the benefit of resistance follows a humpbacked relationship with prevalence. However, cost is now proportional to the frequency of susceptibles (as compared to unity when infecteds reproduce). Furthermore, damage consists of the rate of disease induced mortality plus the density dependent rate of reproduction whose loss now also constitutes damage due to infection. The complex interaction of cost, damage and reduction

in prevalence, all of which vary with the equilibrium state of the host population, obscures the hump-backed relationship. Instead, these factors combine to produce the deceptively simple increasing relationship between optimal investment and the abundance of infecteds scaled by case mortality.

Since these fertility assumptions are closely related to cost assumptions this highlights the key role that cost scenarios play in producing distinct patterns of optimal resistance. This is supported by the contrasting patterns in ESS resistance that result when constitutive and acute cost assumptions are compared in the models of van Boven and Weissing [154]. van Boven and Weissing [154] report that if immune function is costly for infected individuals only and decreases the infectious period, the intuitive expectation that the evolutionarily stable investment in immune function should increase as life span increases still holds. However, for other scenarios, the optimal investment in immunity decreases as the life span of the host increases. They point out that it has been difficult to identify broad patterns valid over a wide range of scenarios. However, in our models here and in those of van Boven and Weissing [154] similar patterns are reported when there are constitutive costs. Furthermore, when there is a departure from the assumption of constitutive costs (i.e. a direct departure through the assumption of acute costs in van Boven and Weissing [154] and an indirect departure through the assumption that infected hosts do not reproduce in this work) the same pattern of increasing investment with increasing lifespan is reported. Taken together then, and with the help of our analytical results here, it is possible to begin to identify broad patterns.

We model investment in immune memory in two ways: *a*) through increased probability of recovering to a permanent immune state (for convenience we call this *optimal life-long immunity*) or *b*) by an increased duration of immunity when recovery always leads to immunity (for convenience, *optimal waning immunity*). We show that in both of these cases optimal investment always increases with disease prevalence. However, it is important to note that despite the expressions for optimal waning and optimal life-long immunity being the same, the models in which they evolve produce different patterns in equilibrium prevalence at high lifespans due to the impact of waning immunity. In particular, a waning immunity term means that there is no very long lived class and this means that it is harder for the host density to approach the carrying capacity which would reduce prevalence because of its association with low host turnover. Avoidance and recovery exhibit remarkably similar optimal investment relationships when the host lacks immune memory yet markedly different relationships when immune memory is present. The key result is that recovery without immune memory is functionally different to recovery with immune memory (i.e. recovery to an immune state is a route to acquired immunity). In the former case it acts to increase the proportion of susceptible hosts

who are vulnerable to reinfection (and therefore follows a humpbacked relationship with disease prevalence), in the latter case it increases the proportion of immunes (and therefore increases with increasing prevalence). This highlights the generality of our results. There are very clear patterns to optimal investment in resistance that are distinct for innate and acquired immunity but within these categories the route is unimportant. Innate resistance lowers prevalence and increases susceptible frequency whereas acquired immunity lowers prevalence and increases immune frequency. Because susceptibles are vulnerable to reinfection but immunes are not this has profound implications for the benefit of resistance. Indeed, this is the only reason why innate resistance has a humpbacked relationship with prevalence while optimal acquired immunity has an increasing relationship with prevalence when infecteds reproduce normally.

Optimal investment has a complex relationship with host lifespan. The dynamic feedbacks (i.e. prevalence when there is no loss of fertility and force of infection when there is loss of fertility) vary with lifespan but optimal investment also depends on density independent terms such as case mortality which may themselves involve lifespan. Accounts of how the various forms of resistance respond to lifespan have been given in van Boven and Weissing [154] and Miller et al. [153] and this has been reviewed in Boots et al. [167]. Maximal optimal investment at intermediate lifespans appears to be a result that is found across models and across resistance forms (though see also the acute cost scenario of van Boven and Weissing [154] which leads to maximal investment at long lifespans). The key exception is the duration of acquired immunity where optimal investment always increases with increasing host lifespan, see Miller et al. [153] and Boots et al. [167]. Our analysis makes it clear that this consistent pattern is not an outcome inherent to the evolution of resistance for any one reason. For example, it occurs for innate resistance when immune memory is lacking (i.e. SIS populations) and the parasite has no effect on fertility where, as discussed above, optimal investment reflects only variation in the benefits of resistance and not the costs. In the absence of a permanent immune state prevalence increases with host lifespan and because benefit is low at both low and high prevalence, investment is maximal at intermediate lifespans. In contrast, when resistance is through permanent acquired immunity (i.e. SIR population), although investment always increases with increasing prevalence, prevalence can be low when hosts have long lifespans (long-lived populations become dominated by immunes when immunity is lifelong) and this leads to maximal investment at intermediate lifespans. In a third, contrasting example when innate resistance evolves to combat parasites causing a loss of host fertility investment is proportional to the abundance of infecteds scaled by case mortality. Abundance increases with increasing lifespan but case mortality decreases and these conflicting selective pressures can lead to

maximal investment at intermediate lifespan but only if recovery is sufficiently fast. These three contrasting examples provide markedly different ways in which the phenomenon of maximal investment at intermediate lifespans can arise. This is an important point, although the phenomena we see may be consistent they result from very different combinations of cost and benefit that arise through ecological feedbacks.

We have shown how the combination of host and parasite characteristics and the ecological interaction between them leads to distinct ecological feedbacks to the evolution of host resistance. Understanding the ecological feedback is essential in accounting for the role that variation in life-history characters such as host lifespan plays in patterns of host resistance. However, intuitive understanding is inevitably gained at the expense of model complexity. It is important to consider the likely effect of additional key interactions like parasite diversity on the phenomenon we describe. For example, the hallmark of innate resistance i.e. the lowering of prevalence and increase of susceptible frequency is likely to be complicated by the presence of additional pathogens and their community dynamics. Therefore, although the results that we present here give a thorough explanation of optimal investment in host resistance in basic epidemiological models, yet they are only a first step in understanding patterns of resistance.

Appendix G

Benefit, cost and optimal investment

In main text equation 5.10 we show that

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = -\left.\frac{C}{B}\right|_{a^*} \tag{G.1}$$

which reveals the correspondence between the singular trait value (through its gradient value $d\omega^m/da^m|*$) and the underlying epidemiological processes. Any resistance singularity on a trade-off with accelerating costs represents optimal investment, ψ^*. The graphical argument in figure $G1$ illustrates why this implies

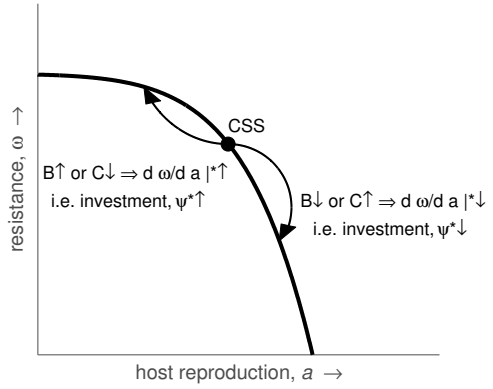

Figure G.1: The gradient of the resistance reproduction trade-off where the singularity can be found is expressed in terms of parameters of the ecological model in the equation $d\omega/da|* = -C/B|*$. The gradient is negative everywhere (investment is costly) and takes large negative values for high reproduction and small negative values for low reproduction (costs are accelerating). Optimal investment, ψ^*, is therefore high or low depending on the ratio of benefit to cost.

$$\psi^* \propto \left.\frac{B}{C}\right|_{a^*} \tag{G.2}$$

Appendix H

Optimal investment in resistance when the pathogen has no effect on fertility

In the main text we consider pathogens who prevent fertility in infected hosts (i.e. $\mu = 0$). In this supporting information we consider both innate and acquired resistance to pathogens who have no impact on host fertility (i.e. $\mu = 1$). We assume that recovery leads to waning immunity and never results in an immediate return to a susceptible state (i.e. $\nu = 1$). Equation 5.10, main text, with $\mu = 1$ is

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = \left.\frac{1 - D\frac{\partial p_I^m}{\partial a^m}}{D\frac{\partial p_I^m}{\partial \omega^m}}\right|_{a^*} \tag{H.1}$$

The next step is to use the proxy for mutant prevalence $\tilde{p}_I^m = T_I/T_H$. When $\gamma > 0$ a mutant can make infinitely many return visits to the epidemiological states i.e. $T_I/T_H = \sum_{i=1}^{\infty} T_{I_i}/T_{H_i}$ where the i's represent the mutant hosts's successive visits to the infected state. However, as mentioned in Boots and Bowers [156], when there is only one route back to susceptibility we can use geometric series to factorise these terms, for example, $\sum_{i=1}^{\infty} T_{I_i} = \phi T_{I_1}$. Furthermore, the factor, ϕ, is the same for each class i.e. $T_H = \phi(T_{S_1} + T_{I_1} + T_{R_1})$, so that, $\tilde{p}_I^m = T_{I_1}/(T_{S_1} + T_{I_1} + T_{R_1})$, i.e. we need only consider the average duration of a mutant's first visit to each of the epidemiological states (but note that this applies as long as there is only one route back to susceptibility).

When $\nu = 1$ the expected time spent by a mutant in each state before leaving that particular state is

$$T_{S_1} = \frac{1}{b + \beta^m I^r} \tag{H.2}$$

$$T_{I_1} = \frac{\beta^m I^r}{b + \beta^m I^r} \frac{1}{\alpha + b + \gamma^m} \tag{H.3}$$

$$T_{R_1} = \frac{\gamma^m}{\alpha + b + \gamma^m} \frac{\beta^m I^r}{b + \beta^m I^r} \frac{1}{b + \delta^m} \tag{H.4}$$

This leads to the following proxies for mutant frequencies

$$\tilde{p}_S^m = \frac{(\alpha + b + \gamma^m)(b + \delta^m)}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r (b + \delta^m) + \gamma^m \beta^m I^r} \tag{H.5}$$

$$\tilde{p}_I^m = \frac{(\beta^m I^r)(b + \delta^m)}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r (b + \delta^m) + \gamma^m \beta^m I^r} \tag{H.6}$$

$$\tilde{p}_R^m = \frac{\gamma^m \beta^m I^r}{(\alpha + b + \gamma^m)(b + \delta^m) + \beta^m I^r (b + \delta^m) + \gamma^m \beta^m I^r} \tag{H.7}$$

so that

$$\left.\frac{d\omega^m}{da^m}\right|_{a^*} = -\left(\alpha \frac{\partial \tilde{p}_I^m}{\partial \omega^m}\right)^{-1} \tag{H.8}$$

for $\omega \in (\beta, \gamma, \delta)$.
Differentiating equation $H.6$ with respect to the various forms of resistance leads to

$$\frac{\partial \tilde{p}_I^m}{\partial \beta^m} = \frac{1}{\beta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{\beta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{\beta^m}\tilde{p}_R^m = \frac{1}{\beta^m}\tilde{p}_I^m \tilde{p}_S^m \tag{H.9}$$

$$\frac{\partial \tilde{p}_I^m}{\partial \gamma^m} = -\tilde{p}_I^m \frac{1}{\alpha + b + \gamma^m}\tilde{p}_S^m - \tilde{p}_I^m \frac{1}{\gamma^m}\tilde{p}_R^m = -\frac{1}{\alpha + b + \gamma^m}\tilde{p}_I^m (\tilde{p}_S^m + \frac{\alpha + b + \gamma^m}{\gamma^m}\tilde{p}_R^m) \tag{H.10}$$

$$\frac{\partial \tilde{p}_I^m}{\partial \delta^m} = \frac{1}{b + \delta^m}\tilde{p}_I^m - \tilde{p}_I^m \frac{1}{b + \delta^m}\tilde{p}_S^m - \tilde{p}_I^m \frac{1}{b + \delta^m}\tilde{p}_I^m = \frac{1}{b + \delta^m}\tilde{p}_I^m \tilde{p}_R^m \tag{H.11}$$

and substituting into equation $H.8$ leads to expressions for optimal investment in the different routes to resistance.

Avoidance

$$\left.\frac{d\beta^m}{da^m}\right|_{a^*} = -\left(\alpha\frac{\partial\tilde{p}_I^m}{\partial\beta^m}\right)^{-1} \tag{H.12}$$

$$\iff \left.\frac{1}{\beta^m}\frac{d\beta^m}{da^m}\right|_{a^*} = -\left(\alpha\tilde{p}_I^m\tilde{p}_S^m\right)^{-1} \tag{H.13}$$

$$\implies \psi^* \propto \alpha\tilde{p}_I^m\tilde{p}_S^m \tag{H.14}$$

where investment, ψ^*, is in the natural logarithm of avoidance resistance (since $1/\beta^m(d\beta^m/da^m) = d\ln\beta^m/da^m$). Expression H.14 for optimal investment in avoidance resistance appears as the $B1$ SIR in table 5.1 (but note that expression H.14 is correct regardless of the value of waning immunity). The SIS entry requires analogous work for the model which assumes that $\nu = 0$).

Recovery

In the case of recovery, for the $SIRS$ model, we also assume that $\delta = 0$ (i.e. recovery to a permanent immune state)

$$\left.\frac{d\gamma^m}{da^m}\right|_{a^*} = -\left(\alpha\frac{\partial\tilde{p}_I^m}{\partial\gamma^m}\right)^{-1} \tag{H.15}$$

$$\iff \left.\frac{1}{\alpha+b+\gamma^m}\frac{d\gamma^m}{da^m}\right|_{a^*} = -(\tilde{p}_I^m(\tilde{p}_S^m + \frac{\alpha+b+\gamma^m}{\gamma^m}\tilde{p}_R^m))^{-1} \tag{H.16}$$

$$= -(\tilde{p}_I^m\tilde{p}_S^m(1 + \frac{\alpha+b+\gamma^m}{\gamma^m}\frac{\tilde{p}_R^m}{\tilde{p}_S^m}))^{-1} \tag{H.17}$$

$$= -(\frac{1}{b}\tilde{p}_I^m\tilde{p}_S^m(b+\beta I)^{-1} \tag{H.18}$$

$$= -(\frac{1}{b}\tilde{p}_I^m\tilde{p}_S^m(b\frac{H}{S} + \alpha\frac{I}{S})^{-1} \tag{H.19}$$

$$= -(\tilde{p}_I^m(1 + \frac{\alpha}{b}\tilde{p}_I^m)^{-1} \tag{H.20}$$

$$\implies \psi^* \propto \tilde{p}_I^m(\frac{\alpha}{b}\tilde{p}_I^m + 1) \tag{H.21}$$

where investment, ψ^*, is in the natural logarithm of the infectious period and hence recovery resistance (since $1/(\alpha+b+\gamma^m)(d\gamma^m/da^m) = d\ln(\alpha+b+\gamma^m)/da^m$). Ex-

pression $H.21$ for optimal investment in recovery resistance appears as $C1$ SIR in table 5.1 (the SIS entry requires analogous work for the model which assumes that $\nu = 0$).

Duration of immunity

$$\left.\frac{d\delta^m}{da^m}\right|_{a^*} = -\left(\alpha\frac{\partial\tilde{p}_I^m}{\partial\delta^m}\right)^{-1} \tag{H.22}$$

$$\iff \left.\frac{d\delta^m}{da^m}\right|_{a^*} = -\left(\frac{\alpha\gamma}{(b+\delta)^2}\tilde{p}_I^m\tilde{p}_I^m\right)^{-1} \tag{H.23}$$

$$\implies \psi^* \propto \alpha\gamma\tilde{p}_I^m\tilde{p}_I^m \tag{H.24}$$

where investment, ψ^*, is in the duration of immunity, $1/(b+\delta)$. Expression $H.24$ for optimal investment in the duration of acquired immunity appears as $B4$ in table 5.1 ($B3$ in table 5.1 requires analogous work for the model that assumes that $\delta = 0$ and $\nu = \nu(a)$).

Appendix I

A proxy for invasion fitness

In this section we demonstrate that replacing mutant prevalence by the expected time a mutant spends infected (and similarly for susceptible frequency and immune frequency) creates a proxy for invasion fitness.

Firstly, if the lifetime reproduction of an invading mutant phenotype, R, is greater than 1, then the invading mutant population will grow. Therefore the condition, $R > 1$, must be met for a mutant to succeed and for this reason it is also an established proxy for invasion fitness [190]. The full condition for the model given by equations $5.1 - 5.3$ is

$$R = T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) > 1 \tag{I.1}$$

Here we show that given that condition I.1 is a proxy for invasion fitness then condition 4.4 and condition 5.6 are also proxies

$$T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) > 1 \tag{I.2}$$

$$\Leftrightarrow T_S^m(a^m - qH^r) + T_I^m(a^m - qH^r) + T_R^m(a^m - qH^r) - 1 > 0 \tag{I.3}$$

$$\begin{aligned}\Leftrightarrow T_S^m(a^m - qH^r - b) + T_I^m(a^m - qH^r - b - \alpha) + T_R^m(a^m - qH^r - b) \\ + T_S^m b + T_I^m(b + \alpha) + T_R^m b - 1 > 0\end{aligned} \tag{I.4}$$

$$\Leftrightarrow T_S^m(a^m - qH^r - b) + T_I^m(a^m - qH^r - b - \alpha) + T_R^m(a^m - qH^r - b) > 0 \tag{I.5}$$

where equation I.5 follows from equation I.4 because $T_S^m b + T_I^m(b + \alpha) + T_R^m b = 1$ which is true given the expressions for T_S, T_I and T_R in equations $H.2 - H.4$. Therefore condition 4.4 is a proxy for invasion fitness. Dividing equation I.5 by T_H

produces condition 5.6 which is therefore also a proxy.

Chapter 6

Multiple parasites and the evolution of host resistance

6.1 Preface

The material in this chapter corresponds to a manuscript which is pending submission as,

Donnelly, R., White, A. and Boots, M., 2014 Multiple parasites and the evolution of host resistance, *in preparation*.

I am the lead author in this work.

6.2 Introduction

Hosts are generally subject to attack from multiple parasites [174–176] and this is likely to have important evolutionary implications. The impact of multiple parasites on the evolution of virulence has been well studied [18, 20, 46, 66, 104, 177–179]. These models suggest that parasite diversity selects for higher virulence when there are multiple infections and that the strength of this effect decreases with the relatedness of the parasites [178, 180]. The role of multiple infections in the evolution of host resistance, on the other hand, is not well studied with models often limited to single infections (but see Bonsall and Raymond [181], Jokela et al. [182], Poitrineau et al. [183]). Parasites interact directly through competition for susceptible hosts, but when the host evolves resistance to a focal parasite the extent to which the resistance also counters co-circulating parasites constitutes an additional, less obvious interaction. Therefore, there is likely to be a complex relationship between parasite diversity and patterns of evolved resistance.

Here we examine the evolution of resistance in the context of multiple parasites

using the framework of evolutionary invasion analysis [31, 32] which is based on explicit ecological dynamics. Evolutionary invasion analysis encompasses both density dependent selection where fitness depends on population densities from the ecological system, and frequency dependent selection where an individual's best strategy is contingent on the strategy of others [4]. Selection pressures are therefore a product of ecological processes and feedbacks. Since one parasite population alters the host environment for another and since there are additional within host interactions between parasites, such as competition, it is important to know how patterns of optimal resistance depend on challenge with co-circulating parasites. Once multiple infections are incorporated in models the question of the specificity of resistance naturally arises, with, in particular, cross resistance occurring when an immune response is not specific to one infection. Such cross immunity is very common if not the norm in medical and veterinary disease and also seems common in natural systems in the few examples where it has been studied. For example, cross resistance of a Nuclear Polyhedrosis Virus (NPV) and a Granulosis Virus (GV), in NPV selected fall army worm, *Spodoptera frugiperda*, has been reported in Fuxa [184]. Ferrari et al. [185] show that Pea aphids resistant to *Aphidus ervi* can also resist *A. eadyi* but not a fungal parasite (*Pandora neoaphidis*). These studies and others [186] demonstrate that cross-resistance often occurs and is most likely between related parasites.

There is a large body of work that examines the evolution of immunity in the context of ecological feedbacks to a single parasite [19, 49, 153–155, 157, 167, 187] but relatively few models have considered parasite diversity in the study of host defense. Bonsall and Raymond [181] developed a host parasite model, structured by developmental stage, to explore the ecological and evolutionary dynamics of resistance to different infections. However, the infections in this model are functionally very different having contrasting modes of transmission and the focus is on the effect of developmental stages. Poitrineau et al. [183] explored optimal investment in defence traits against two natural enemies. They analysed the implications to investment of interactions between the defences (interference and synergy) but their analysis was based on a fitness that ignored ecological dynamics. This is also the case for the models of Jokela et al. [182] that focus on the relationship between the effectiveness of defense and optimal allocation. Here we apply an eco-evolutionary approach to explore the question of how multiple challenges to hosts alters selection for resistance. The ecological derivation of host fitness allows population densities from the host-parasite system to influence natural selection and this allows us to provide clear insight into the effect of co-circulating parasites on host resistance.

6.3 Methods

Following Kermack and McKendrick [10], later developed by Macdonald [188] and Anderson and May [169], we assume a host structure based on susceptible, infected and immune sub-populations. Since infection spreads through the population according to the abundance of infecteds and is constrained by the supply of susceptibles, the population structure is a key determinant of the evolutionary dynamics. We define a general infectious disease model with two distinct parasites:

$$\frac{dX}{dt} = aH - qH^2 - bX - \beta_1 XY_1 - \beta_2 X(Y_2 + Y_{21}) + (1-\nu_1)\gamma_1 Y_1 + \gamma_2 Y_2 \quad (6.1)$$

$$\frac{dY_1}{dt} = \beta_1 XY_1 - (\alpha_1 + b + \gamma_1)Y_1 - s\beta_2 Y_1(Y_2 + Y_{21}) \quad (6.2)$$

$$\frac{dY_2}{dt} = \beta_2 X(Y_2 + Y_{21}) - (\alpha_2 + b + \gamma_2)Y_2 + s\beta_2 Y_1(Y_2 + Y_{21}) \quad (6.3)$$

$$\frac{dZ_1}{dt} = \nu_1\gamma_1 Y_1 - bZ_1 - \sigma\beta_2 Z_1(Y_2 + Y_{21}) + \gamma_2 Y_{21} \quad (6.4)$$

$$\frac{dY_{21}}{dt} = \sigma\beta_2 Z_1(Y_2 + Y_{21}) - (\alpha_2 + b + \gamma_2)Y_{21} \quad (6.5)$$

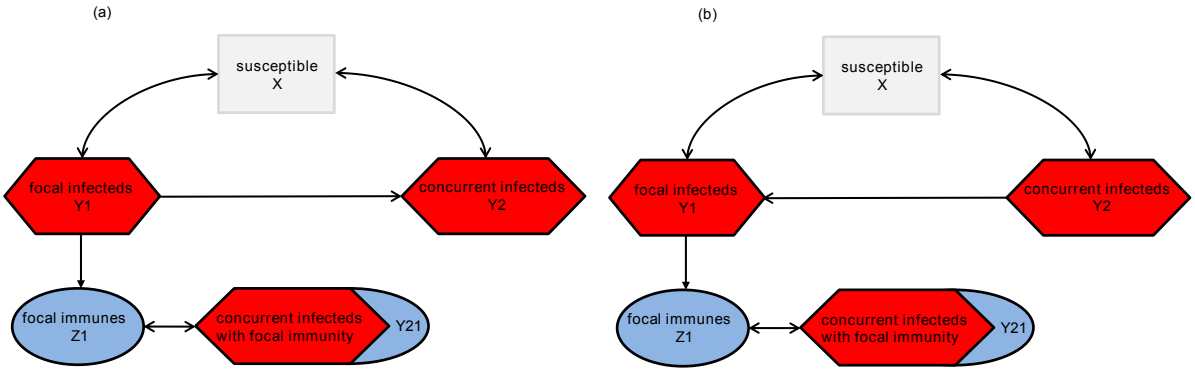

Figure 6.1: Flow chart for the epidemiological process. In *(a)* the co-circulating parasite is more virulent than the focal parasite and therefore individuals move from the focal infection class Y_1 to the co-circulating infection class Y_2 instantly when the co-circulating infection is transmitted to a an individual infected with the focal infection. In *(b)* the focal parasite is more virulent than the co-circulating parasite and therefore individuals move from the co-circulating infecteds class Y_2 to the focal infecteds class Y_1 when the focal infection is transmitted to an individual already infected with the co-circulating infection.

The model compartmentalises the host population into densities of susceptibles, X, focal infecteds, Y_1, co-circulating infecteds, Y_2, hosts with life-long immunity to the

focal infection, Z_1 and hosts that are infected by the co-circulating parasite but are immune to the focal parasite, Y_{21}. For simplicity, there is no direct acquired immunity to the co-circulating parasite, but immunity to the focal infection can carry over to the co-circulating parasite if it is non-specific (this corresponds to $\sigma < 1$). Total host density is given by $H = X + Y_1 + Y_2 + Z + Y_{21}$. All parameters are non-negative and $\nu_1 \in [0, 1]$. All hosts produce susceptible offspring at rate a which is limited by intra-specific crowding, q. Hosts die at natural death rate b. Transmission of infecteds is a mass action process between susceptible and infected types, with transmission coefficient β_1 for the focal infection and β_2 for the co-circulating infection. Infected hosts suffer additional disease induced mortality (virulence) at rate α_1 for the focal parasite and α_2 for the co-circulating parasite. Infected hosts recover at rate γ_1 from the focal infection and γ_2 from the co-circulating infection, and a proportion of recoveries from the focal infection, ν_1, become immune to the focal parasite while the remaining individuals return to a susceptible state. Individuals infected with the less virulent parasite are also susceptible to infection by the more virulent parasite with the more virulent infection replacing the less virulent infection i.e. superinfection [104]. Therefore, if $\alpha_2 > \alpha_1$ the co-circulating parasite superinfects the focal parasite because it has a higher virulence and therefore grows more aggressively in the host and this is the situation represented by equations $1-5$ and represented schematically by figure 6.1*a*. If $\alpha_2 < \alpha_1$ the focal parasite is more virulent and superinfects the co-circulating one and this is represented by figure 6.1*b* (for brevity the equations for this model are not shown but it is simply the above model with the direction of superinfection reversed and a transmission coefficient for the superinfection term of β_1 rather than β_2). The superinfection coefficient s controls the strength of the interaction and for our purposes $0 \leq s \leq 1$ (the less intuitive case where the transmission rate is increased by the presence of a co-circulating infection is not dealt with here).

This general model form can be used to capture a wide range of classical infection scenarios. For example, if $\nu_1 = 0$ the model represents a Susceptible−Infected−Susceptible (SIS) framework, where there is no immune memory and recovered individuals are completely susceptible to both infections. On the other hand if $\nu_1 = 1$ we have the Susceptible−Infected−Recovered (SIR) model with specific ($\sigma = 1$) or non-specific ($\sigma < 1$) life-long immunity (though, for simplicity, the structure due to the co-circulating parasite remains SIS). In the previous example specificity is denoted by σ and if σ is high then specificity is high. In all the other forms of resistance specificity, c, is a parameter in the host trait that resists the co-circulating infection (i.e. $\beta_2 = \beta_2(c)$ for avoidance and $\gamma_2 = \gamma_2(c)$ in the case of recovery) and here high values of c correspond to low specificity (see later for more details). The fundamental forms of host defence can be defined as follows [167]: (i) avoidance

reduces the probability of becoming infected and resistant hosts therefore have a lower transmission rate (β_1), (ii) recovery increases the rate of clearance of infection (γ_1), whereas (iii) tolerance reduces virulence (α_1) (not studied here since it is not a form of resistance). Finally, (iv), acquired immunity increases the probability of inducing acquired immunity (ν_1). Elsewhere the maintenance of induced acquired immunity is defined in single infection models as a decrease in the rate of waning immunity [153]. We first consider routes of innate resistance, i.e. avoidance and recovery (*i* and *ii* above) in an SIS setting and then in an SIR setting with specific life-long immunity and later evolution of acquired immunity itself.

A key measure in the evolution of resistance is disease prevalence, the frequency of infected individuals in the host population. In single infection models, whether the population structure is SI, SIS, SIR or $SIRS$, prevalence at the endemic equilibrium satisfies

$$\alpha \frac{Y}{H} = a - qH - b \tag{6.6}$$

i.e. prevalence multiplied by virulence equals host population turnover. When there are two infections in the population, turnover at equilibrium equals the sum of the prevalences of the two infections weighted by their respective rates of virulence

$$\alpha_1 \frac{Y_1}{H} + \alpha_2 \frac{Y_2}{H} = a - qH - b \tag{6.7}$$

There is strong empirical evidence for the association of resistance with physiological costs through the diversion of resources to the development and maintenance of the resistance. In Fuxa and Richter [136] the percentage of eggs that hatch as well as the number produced per female were all lower in fall armyworm lines selected for resistance to NPV. Longer development time, reduction in egg viability as well as an increase in pupal weight were a consequence of selection for resistance to a granulosis virus in *Plodia interpunctella* in Boots and Begon [57]. In Kraaijeveld and Godfray [137], reduced larval competitive ability in acquiring food in unparasitized *Drosophila melanogaster* is the result in lines selected for improved encapsulation. Blocking glands producing antimicrobial peptides in leafcutter ants results in a decrease in respiration rate in Poulsen et al. [170]. Taken together these studies represent a sound basis for assuming that costs to resistance can be manifested in reduced host reproduction or reduced competitive ability. In this study we assume an association between level of resistance and reproduction rate such that recovery, avoidance and acquired immunity are all positive decreasing functions of

host reproduction rate.

We begin by considering an SIS framework where the focal parasite is less virulent than the co-circulating parasite (i.e. $\alpha_1 < \alpha_2$). Hosts invest in costly resistance, $0 \leq \theta(a) \leq 1$, through avoidance of the focal infection (i.e. $\hat{\beta}_1 = \beta_1(1 - \theta(a))$) and resistance may carry over to the co-circulating infection depending on the specificity of resistance ($0 \leq c \leq 1$, when $c = 0$ the resistance is specific to the focal infection), i.e. $\hat{\beta}_2 = \beta_2(1 - c\theta(a))$. As c increases the resistance becomes more general.. Alternatively resistance can be through recovery (i.e. $\hat{\gamma}_1 = \gamma_1(1 + \theta(a))$ and $\hat{\gamma}_2 = \gamma_2(1 + c\theta(a))$). Similarly the focal infection can be more virulent than the co-circulating parasite for each of the above cases (i.e. $\alpha_1 > \alpha_2$). When it comes to an SIR framework we consider all of the above cases but only when the focal parasite is less virulent than the co-circulating parasite. Finally in an SIR framework resistance may be through acquired immunity, corresponding to $\hat{\nu}_1 = \theta(a)\nu$. We view specificity of acquired immunity not in terms of the probability of clearance of the co-circulating infection to an immune state, but rather as the decrease in transmissability of the co-circulating infection to individuals who are immune to the focal infection. For this reason, specificity in acquired immunity is a fixed coefficient, σ, in equations 6.4-6.5 with $\sigma = 1$ when resistance is specific or $\sigma < 1$ when it is not specific. For simplicity, we do not allow the less intuitive case where σ exceeds 1 (i.e. resistance developed to counter a focal parasite is more effective against a co-circulating parasite).

6.4 Results

Evolutionary invasion analysis allows conclusions to be made about phenotypic evolution based on the properties of invasion fitness. Invasion fitness can be derived through a linear stability analysis of a mutant ecological model in a population consisting of residents at their population attractor (usually a stable point equilibrium). If the steady state corresponding to no mutants but positive residents is unstable then the mutant can invade. Hence, eigenvalues (of the coefficient matrix, A, of the linearised system, $\dot{x} = Ax$) determine the invasion potential of the mutant and in particular the dominant eigenvalue is a measure of invasion fitness. When a mutant host invades a resident population that is challenged by multiple infections, high dimensionality means it is not straightforward to derive an expression for invasion fitness directly. Instead, following the next generation method [21], the linearised system can be decomposed into two matrices, $A = F - V$. If the largest absolute value of the eigenvalues of the matrix FV^{-1} is greater (smaller) than 1, then by the next generation theorem [189, 190] the invasion fitness is positive (negative), but note that conditions on the matrices F and V apply, see van den Driessche and

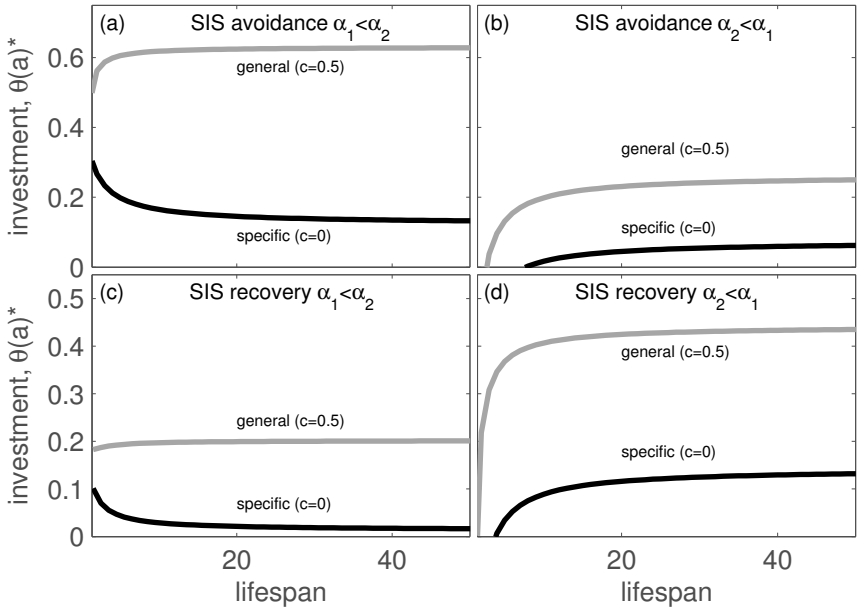

Figure 6.2: Optimal investment in specific and non-specific resistance in an SIS structured host population. In (a) and (b) the function of the resistance is avoidance. In (c) and (d) the function of the resistance is recovery (i.e. increased rate of disease clearance). In (a) and (c) resistance is evolved to counter the avirulent infection while in (b) and (d) resistance is evolved to counter the virulent infection. In all cases both infections will be equally countered when resistance is completely general ($c = 1$). Parameters were: $q = 0.1$ $\beta_1 = 2$ $\beta_2 = 4$ $\alpha_1 = 2$ $\alpha_2 = 8$ with $s = 0.45$, in the case of evolving avoidance $\hat{\beta}_i = \beta_i(1 - 0.5\theta)$ $\gamma_1 = \gamma_2 = 0.35$ and in the case of evolving recovery $\hat{\gamma}_i = \gamma_i(1 + 2.5\theta)$ $\gamma_1 = \gamma_2 = 1$. In all cases $\theta(a) = 1 - (a^\mu)/(a^\mu_{max})$ with $a_{max} = 1.9$ and $\mu = 12$.

Watmough [189].

We use the next generation method to formulate a proxy for invasion fitness, denoted $s_r(m)$ for the set of models outlined in the *Methods* section. Under the assumptions of adaptive dynamics [31, 32] a population will evolve through small mutations in the direction of the gradient of the invasion fitness and may reach an evolutionary singularity where the mutant derivative of invasion fitness is zero. Evolutionary singularities can be classified according to their evolutionary and convergence stability properties. If a singularity is both evolutionary and convergence stable it is an uninvadable evolutionary attractor and an end point of evolution. We wish to examine how such singularities change when life-history and epidemiological parameters are varied.

Proxies for invasion fitness, $s_r(m)$, of hosts bearing a mutant investment phenotype, $\theta^m(a^m)$, are obtained for each case. Using the invasion fitness proxies to locate the evolutionary attractors we can show how the evolved level of the resistance phenotype varies with host lifespan, see figure 6.2a-d. This can be shown when resistance is specific (black curves, figure 6.2a-d) and also when resistance is

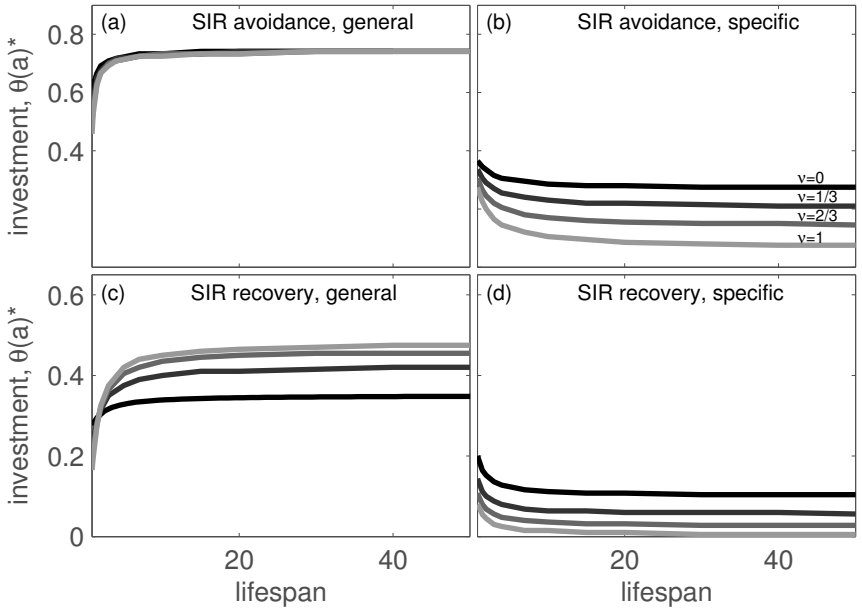

Figure 6.3: Optimal investment in specific and non-specific resistance in an SIR structured population developed to counter the avirulent infection. In (a) and (b) resistance is through avoidance while in (c) and (d) resistance is through increased recovery. The proportion of recovered individuals entering the immune class is ν while the proportion returning to a susceptible state is $1-\nu$. As ν increases above 0 towards 1 the population becomes SIR (grey through to light grey curves). In (a) and (c) $c = 0.5$ while in (b) and (c) $c = 0$. In (a) and (b) the trade-off exponent is $\mu = 18$, in (c) and (d) $\mu = 24$. For all other parameter values and the trade-off form see caption, figure 6.2.

non-specific (grey curves, figure 6.2a-d). It can also be shown when resistance is through avoidance (figure 6.2a & b) and when resistance is through recovery (figure 6.2c & d), when the resistance is developed primarily to counter a relatively avirulent focal infection (figure 6.2a & c) or to counter a relatively virulent focal infection (figure 6.2b & d). The resulting graphs indicate that regardless of the route of innate resistance, investment increases with host lifespan except when it is specific to an avirulent infection.

Focusing on the case where resistance evolves to counter an avirulent focal infection we show that these results extend to an SIR framework, arising through the presence of acquired immunity specific to the avirulent focal infection (i.e. $\sigma = 1$), see figure 6.3a & c for avoidance, and see figure 6.3b & d for recovery. As the proportion of immune individuals in the population increases, from $\nu = 0$ represented by a black curve to $\nu = 1$ represented by a light grey curve, there is no qualitative change, though the overall magnitude of investment tends to decrease. This is because recovery to immunity tends to decrease prevalence and hence reduces the selection pressure for investment in resistance. Finally, we analyse optimal acquired immunity developed to counter the avirulent parasite. Here, the mutant invest-

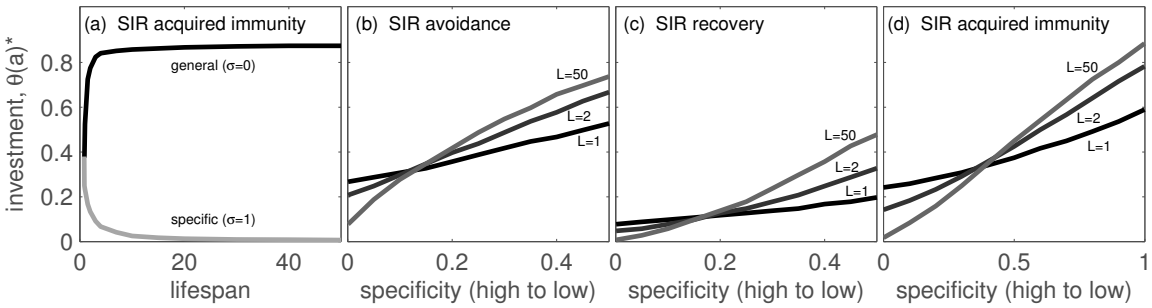

Figure 6.4: Optimal investment in specific (black curve) and non-specific (grey curve) acquired immunity is given in (a). In (b), (c) and (d) optimal investment for a range of values of specificity is given for avoidance, recovery and acquired immunity respectively in an SIR structured population ($\nu = 1$ throughout). In each case three separate curves are displayed for the following values of host lifespan, $1/b = 1$ (black curve), $1/b = 2$ (dark grey curve) and $1/b = 50$ (grey curve). (b), (c) and (d) indicate that there is a critical value of specificity below which high lifespans are associated with higher investment than low lifespans. On the other hand, beyond this critical value low lifespans are associated with higher investment than high lifespans. In (a), (c) and (d) the trade-off exponent is $\mu = 24$ and in (b) $\mu = 18$. For all other parameter values and the trade-off form see caption, figure 6.2.

ment phenotype is $\nu_1^m(a^m)$ and immunity extends to the virulent infection if $\sigma < 1$. When immunity is non-specific, investment increases with increasing lifespan, when immunity is specific investment decreases with increasing lifespan, see figure 6.4a.

As a whole, the results show that resistance to a relatively avirulent focal infection in the presence of a co-circulating virulent infection varies with host lifespan in a manner that is dependent on the specificity, but not the route of resistance. In general, investment increases as the level of specificity in resistance decreases (figure 6.4b-d) . We provide a further illustration of this in figure 6.4b where curves are given for different lifespans. Investment is greater at low lifespans when resistance is specific (c is low) but investment is greater at long lifespans when resistance is relatively general (c is high). Therefore, there appears to be a level of specificity for each form of resistance below which investment decreases with increasing host lifespan and above which investment increases with increasing host lifespan. This transition occurs for relatively small values of specificity for the innate forms of resistance (i.e. avoidance and recovery) compared to the relatively high value of specificity at which it occurs for acquired immunity.

6.5 Discussion

It is clear that in natural settings individuals are typically challenged by multiple parasites, but to date theory on the evolution of resistance has focused on single infections. In this work we have developed a series of models that have examined the impact of multiple parasites on the evolution of resistance. Specifically we have made the assumption that parasites coexist as a consequence of superinfection which allows a fast growing parasite to replace a slow growing parasite in individuals who become doubly infected. Our models have shown that co-circulating parasitism dramatically impacts on the evolution of resistance to a focal parasite. In particular, the specificity of the resistance with respect to co-circulating parasites is critical to the outcome. A key, intuitive, result is that investment in resistance increases as the immune response becomes more general. There has been considerable interest in how host life-span impacts on immune investment and our models show that additional parasites in the host population has profound effects on how resistance changes as life-span increases. As a whole, our work emphasises the importance of considering multiple parasites when determining optimal immune resistance.

Risk of infection by pathogens and parasites has led hosts to evolve a wide range of defence mechanisms from behavioural strategies [191] to the bio-chemical cascades of the complement system and the memory B and T cells of adaptive immunity [109, 110]. Intuition suggests that the longer a host lives the more it is likely to benefit from immunity. This observation has been used to explain macro-evolutionary patterns of investment such as the lack of acquired immunity in invertebrates [114, 120] and is supported by a number of empirical studies. For example, a positive correlation between immunity and lifespan in avian hosts has been demonstrated for humoral, cell mediated, and constitutive immune responses [116–119]. Theoretical models that have examined the evolution of resistance in the face of a single parasite make the assumptions underlying this intuition explicit. They have provided some support for this pattern but also deviate from it in important ways [153, 154, 167, 187]. For example, optimal resistance in hosts capable of permanent acquired immunity can be maximal at intermediate lifespan [167, 187] and in the case of innate resistance this can be true even in the absence of acquired immunity [153, 187]. However, a key aspect of these models is that host populations are burdened by only one infection, and in this work we find that co-circulating parasitism leads to fundamentally different predictions.

When a host population is challenged by multiple parasites the investment in immunity is critically dependent on the specificity of the defence. When the resistance is relatively general, then investment increases with host lifespan. On the other hand when immunity is specific the pattern of investment relative to host lifespan depends

on the nature of the co-circulating parasite. If the co-circulating parasite poses less danger to the host than the focal infection, then investment increases with lifespan. In contrast, if the second parasite is more severe, then specific immune investment decreases as host lifespan increases because the ratio of co-circulating prevalence to focal prevalence increases. These patterns are true in our model when the evolving resistance is innate in a host incapable of immune memory, is innate in a host responding additionally with immune memory or when the evolving resistance is itself acquired. This is an important insight since it shows that the life-history patterns will depend on the nature of the co-circulating parasite, and the specificity of the response, but not the mode of resistance itself, which is in stark contrast to single infection models where patterns fundamentally depend on the mode of resistance [153, 154, 167, 187]. A key implication of our work is that the classic idea that more investment should occur in longer-lived hosts is generally supported when there are multiple parasites.

What are the processes that lead to these critically different patterns (i.e. in the effect of host lifespan on optimal immune defence) when host are faced by multiple rather than single parasites? Single infection models deviate from the intuition that investment increases with lifespan because of two important effects that are undermined by the presence of co-circulating infections. In single infection models, optimal investment that is maximal at intermediate lifespans [153] is a hallmark of innate resistance because it is characterised by the return or maintenance of individuals in a susceptible state as opposed to the conversion of them into an immune state [187]. Since susceptibles are vulnerable to reinfection which is likely at high levels of prevalence the benefit of innate resistance is low at high prevalence and therefore low at high lifespans (in SIS models prevalence increases with increasing host lifespan). With multiple parasites and superinfection, more virulent parasites take over hosts infected with less virulent parasites. When hosts live longer, the period during which these conversions occur is longer and this favours the virulent parasite. However, the higher virulence of these parasites also acts to reduce infectious period and as a consequence, prevalence does not rise to the high levels that are seen in equivalent single infection models. As such, optimal investment increases with lifespan in the face of multiple infections and superinfection in models where it would be maximal at intermediate lifespans without the co-circulating infection.

There is a second process that comes into play once there is permanent immunity to the parasite. In single infection models where the host is long-lived, permanent immunity leads to high host density. When host density approaches the carrying capacity there is little host turnover and prevalence levels are low. Therefore long-lived host populations with permanent immunity have little need for resistance because prevalence is low [153, 167, 187]. For this reason a long-lived immune class can de-

crease the need for immunity in general at high lifespans. However, crucially, when there are multiple infections there may no longer be a long-living permanent immune class since immune individuals are susceptible to infection by the co-circulating parasite. Therefore, when acquired immunity evolves in the face of multiple parasites and superinfection, just as for innate immunity, optimal investment is higher in long-lived host populations in models where it would be maximal at intermediate lifespans without the co-circulating infection.

There is one important exception to our general prediction that investment in immunity rises with host lifespan. When the co-circulating parasite is more virulent and the evolving response is specific to the focal parasite, then investment decreases with increasing lifespan. The simple interpretation for this result is that there is little fitness benefit to investing resources into fighting the lesser of your enemies. If the co-circulating parasite is more virulent then it is the superinfector and it is favoured at high lifespans. Therefore the benefit of specific resistance to the focal parasite, which by definition is not effective against the co-circulating parasite, diminishes as lifespan increases.

In conclusion, there is considerable nuance to the relationship between optimal investment in immunity and host lifespan in single infection models [153, 167, 187], but here we have presented a strong argument that this nuance is likely to be lost as greater realism in the form of parasite diversity is incorporated into models. Instead it is the classic idea that long-lived hosts invest more in immunity that is supported when a key aspect of natural complexity in host-parasite systems, diversity in the parasite burden of the host population, is included.

Chapter 7

Discussion

Crises in public health such as emerging diseases or deadly outbreaks, for example, the latest corona-virus (Middle East respiratory syndrome) and the recent ebola epidemic in West Africa, generate global news coverage and make the need for the study of infectious disease obvious to all. Agricultural and wild life disease make for a less dramatic story but one, nevertheless, of fundamental economic importance as we struggle to feed an increasing population (for example, the foot and mouth outbreak in the UK caused disruption to farm systems and led to widespread slaughter of livestock [192]). Furthermore, the hidden role that infectious disease plays in the stability of ecological communities demonstrates that infectious disease is a pervasive topic that demands our understanding and one that must be assessed in its ecological context. In this body of work we have focused on the core theory of the evolutionary ecology of infectious disease. We have produced a range of analytical results that can be interpreted together to explain key relationships in the evolution of hosts and parasites in a novel and insightful way.

In chapter 2 we introduced the theory of adaptive dynamics using the example of the evolution of virulence in its basic form. The results in this section are well established yet even here traditional interpretations are still asserted. A common view is that shorter host lifespans select for more aggressive parasites because their high natural mortality means that the host will die rapidly anyway. This suggests that the cost of harmful virulence is less important if natural mortality is high. In fact the basic model demonstrates that parasite exploitation is correlated with the density of susceptibles. This is because the benefit of increased transmission depends on susceptible density (i.e. there is little benefit from increased transmission if there are no infectable hosts). Therefore, in contrast to the traditional explanation, exploitation is expected to be high when natural mortality is high because of the higher susceptible density (i.e. a consequence of the equilibrium expression for susceptible density, $X = (\alpha + b + \gamma)/\beta$, is that X increases as b increases) and not directly because virulence is less significant to individuals when hosts die quickly of

natural causes.

Empiricists have recently emphasised the context dependent nature of virulence [71–73] and in chapter 3 we presented a model of the evolution of virulence that links the virulence experienced by the host to its condition, which we assume is related to total host density. As the level of stress that a host experiences (because of the high demand on shared resources) is unlikely to be even throughout a season we allowed host density, and hence virulence, to fluctuate in a seasonal manner by making the rate of host reproduction seasonal. The extent to which host density feeds back to virulence can be specified, and in the limit of no feedback from host density to virulence (i.e. the basic SIR model with host self-limitation and our DDV model with $c = 0$) we show why periodic fluctuations have no impact on selection for virulence. When the feedback between host density and virulence is included, however, there is an asymmetry between the effects of high reproduction in the up season and low reproduction in the down season on host density. This asymmetry increases as the amplitude of seasonality increases. The asymmetry is caused by diminishing returns on increases of the reproduction rate in raising the equilibrium host density (because high density is harder to achieve with DDV since it corresponds to an amplified rate of disease induced death). The result is that average densities are lower when densities fluctuate seasonally. Although the lower average susceptible density makes transmission less beneficial the lower total host density makes it less costly, and it is always the case that the latter effect is greater in magnitude than the former. The result is that investment in density dependent virulence increases with increasing seasonality.

Previous studies have claimed that seasonality of host populations is likely to select for less virulent parasites since virulent strains will be more likely to go extinct through demographic stochasticity in the down season [72]. This is essentially due to random drift [5] with the more virulent phenotypes being subject to a higher probability of extinction. This effect should be seen in finite populations with seasonality regardless of the density dependence of virulence. In contrast, our results are purely deterministic and should be the sole effect in sufficiently large populations. Therefore in finite populations when there is no DDV we expect to see only the decrease in evolved virulence under seasonality and this decrease is proportional to the equilibrium host density in the down season (in population genetical models of random drift heterozygosity is proportional to the population size [5]). In finite populations when there is DDV we expect to see a decrease in virulence due to drift and an increase in virulence due to the asymmetric effect of down and up seasons on host density. Moreover the extent to which there will be a net increase or decrease depends critically on the size of the infected host density in the down season.

Invasion fitness for models of the evolution of parasite virulence is simply the

growth rate of hosts infected with the mutant parasite in an equilibrium resident population. However, invasion fitness for the evolution of host phenotypes is more complex since the growth rate of mutants in all of the epidemiological states must be considered. In chapter 4 we synthesised the empirical and theoretical literature on how optimal levels of host resistance are expected to depend on variation in host and parasite lifespans. In simple theoretical models it has been observed that investment in resistance is often maximal at intermediate host lifespans [153, 154]. In our novel synthesis new theory is included on the relationship between optimal acquired immunity and host lifespan when resistance is associated with a cost through decreased reproduction rate that clearly explains this result. When acquired immunity is permanent, immunes dominate the population at high lifespans and therefore the selection pressure for resistance is weak. In chapter 5 the methods of chapter 4 are developed and extended. They are applied in a systematic, comparative approach that explains comprehensively optimal resistance for a combination of host and parasite types. The comparative approach makes the implication of host factors (such as immune memory capability) and parasite factors (such as the effect of infection on host fertility) to the evolution of resistance explicit. It emphasises key differences in the evolutionary dynamics of innate and acquired immunity. Innate immunity fundamentally returns (or maintains) individuals to a susceptible state. There is a high risk of reinfection if disease prevalence is high. For this reason innate resistance is maximal at intermediate prevalence. Acquired immunity fundamentally moves individuals to an immune state where they are protected from reinfection. Therefore, in contrast to innate resistance, acquired immunity always increases with increasing prevalence. Furthermore the results of chapter 5 emphasise key differences in the dynamics of resistance to parasites who prevent fertility in their infected hosts (we call such parasites *fertility-reducing*) and parasites that have no effect on fertility (*fertility-benign* parasites). All classes of host pay the reproduction cost equally when parasites are *fertility-benign* and therefore costs do not vary with life-history parameters so that optimal investment in resistance reflects only variation in the benefit of resistance. However, for *fertility-reducing* parasites the cost depends on the frequency of individuals who are not infected as they are the only hosts who effectively pay the costs. Therefore there is an additional feedback based on the frequency of uninfected hosts when parasites reduce fertility and this is critical to the qualitative patterns that result.

In the literature several papers have been published on immunity and lifespan [153–155]. Though these papers present important results and provide some explanation of the results, they lack a degree of insight because of the absence of analytical expressions for investment. By introducing an expression for fitness that can be partitioned into the different model classes it is possible to understand the

selective components of optimal resistance. The exact detail, i.e. the exact form of the expressions for optimal immunity, as well as the figures to illustrate them are then produced by combining proxy expressions for fitness with this approach. Both van Baalen [155] and van Boven and Weissing [154] used a classical life-history approach based on reproductive values [193] to explore the evolution of resistance. However, when density dependence regulates the host population the limitations of this approach becomes clear, no analytical expression can be obtained for the optimal trait without at least specifying a trade-off. Without an analytical expression it is very difficult to explain the observed results since the dynamics of resistance are complex compared to virulence. Our evolutionary invasion analysis approach allows such expressions to be found and intuitive explanations to be derived. One limitation of this approach is that it does not take account of transient dynamics which are incorporated in the reproductive value approach [30]. The importance of transient dynamics depends on the extent to which a separation of evolutionary and ecological times scales is justified (which is assumed in evolutionary invasion analysis, see Geritz et al. [31], Metz et al. [32]), however Day and Gandon [43] have proposed a method for relaxing the assumption of a separation of time scales. Applying such a method to examine the evolution of host resistance is a topic for future research.

In chapter 6, the insights from the comparative study of the evolution of resistance in chapter 5 are used to explain contrasting results when more than one parasite circulates in the host population. Analytical results for specific parameter sets and trade-offs reveal that investment in resistance tends no longer to be maximal at intermediate lifespans when a co-circulating parasite (interacting with the focal parasite according to superinfection assumptions) is present in the host population. Investment increases with increasing host lifespan except for the particular case where the co-circulating parasite is more virulent and resistance to the focal parasite leaves it unaffected (i.e. resistance is completely specific to the less virulent of the parasites). In this case investment in resistance to the focal parasite always decreases with increasing lifespan. The effect of the superinfecting co-circulating parasite can be interpreted through the ways in which the multiple infection results differ from the single infection models.

Much has been written on the implication of parasite diversity to the evolution of virulence [20, 104]. From these studies it is clear that parasite diversity has a significant impact on the evolution of epidemiological traits. However, to our knowledge, this is the first attempt to model the effect of parasite diversity specifically on the evolution of resistance (but see Bonsall and Raymond [181], Jokela et al. [182], Poitrineau et al. [183] for models of the evolution of defense with multiple parasites or enemies more generally). Models of resistance that incorporate para-

site diversity must take account of the specificity of immune response and indeed this is a recurrent theme in empirical studies (see, for example, Fuxa and Richter [136], Kraaijeveld and Godfray [137]). We show that the level of specificity in how the immune response, developed primarily to counter the focal parasite, affects the co-circulating parasite is critical to the evolutionary dynamics of resistance. It has been noted many times that simple intuition suggests that investment in resistance should increase with the expected duration of host lifespan [110] but single infection models have shown that the reality is more nuanced (see van Boven and Weissing [154] and Miller et al. [153]) but still comprehensible (see chapters 4 and 5 of this work). We show here that when co-circulating parasites follow a superinfection dynamic the simple intuition turns out to be correct in many situations. The only exception is when resistance is specific to a relatively less virulent parasite. This is perhaps an obvious exception since there is little point in expending resources on resistance to the focal parasite if it is less threatening and more likely to be dominated at high lifespan by the co-circulating parasite because of superinfection. Nevertheless it is a result that is not likely to be considered without a careful modelling approach and often this is where mathematical modelling makes the biggest contribution.

The results from single infection models have been crucial in interpreting the multiple infection evolutionary dynamics since they present a well understood simpler model for comparison. This has also been true for the evolution of virulence and the evolution of density dependent virulence in seasonal host populations. This highlights the bottom up approach we have taken to incorporating complexity in models of evolutionary epidemiology. In accordance with this approach it is worth considering what the implications of our study are for the co-evolution of host and parasite as this is likely to suggest future extensions to this body of work.

7.1 Coevolution of parasite virulence and host resistance

Evolutionary invasion analysis has been successful in understanding the coevolution of parasite virulence and host resistance [102, 194]. Best et al [102] focused on whether coevolutionary branching could occur, but also on how the coevolutionary CSS depends on life-history parameters. Here we use the results and insight from our studies to discuss and to extend these findings.

Coevolutionary models of evolutionary invasion analysis have shown how ecologically based selection pressures can guide the co-evolving host parasite population towards a co-evolutionary attractor if the attractor is a co-CSS (or more generally

with diminishing returns on investment in both host and parasite phenotypes [195]). The coevolutionary attractor represents optimal host and parasite fitness. However, as we have seen, the expression for optimal investment in resistance involves both prevalence and virulence both of which are determined by the phenotypic value of the evolving parasite. Equally, optimal virulence depends on susceptible density which is a function of virulence, recovery and transmission rate which are determined by the evolving host (i.e. optimal virulence is an increasing function of avoidance and recovery but is independent of acquired immunity). Therefore there are coevolutionary feedbacks between the evolving host phenotype and optimal parasite virulence as well as between the evolving parasite phenotype and optimal host defence. The nature of these feedbacks is potentially central to the explanation of coevolutionary dynamics because coevolutionary feedbacks result in a target for coevolutionary trajectories that shifts as the populations evolve.

In order to interpret the consequences of the coevolutionary feedbacks let us assume that parasites evolve at a faster rate than their hosts (the generation time of parasites is generally far shorter than hosts [110]). Therefore, we will assume that the parasite is at its optimal value when we consider host mutations. If there is a positive coevolutionary feedback then the coevolutionary attractor will shift to successively higher phenotypic values of the parasite as the host evolves and to higher values of the host phenotype as the parasite evolves. An example of this occurs when the *clearance rate to immunity* co-evolves with parasite virulence. Starting from low resistance, since prevalence is initially non-zero the host will be selected to increase its resistance. As host resistance increases there will be selection for an increase in parasite virulence (because equilibrium susceptible density will increase as recovery increases). As parasite virulence increases the host will be selected to yet higher values of resistance (because the successful parasite invasions leads to higher prevalence as a result of the increase in the parasites lifetime reproduction). In this manner virulence and resistance through *clearance to immunity* are expected to co-evolve to high levels of optimal resistance and optimal virulence which can corresponds to high levels of disease prevalence, see figure 5.3 (b) $i)$ and 5.4 (b) $i)$.

In the case of co-evolving innate resistance and virulence the feedback is slightly more nuanced because of the hump-backed relationship between investment and resistance and disease prevalence, see figures 5.2 (a) $i)$ and (b) $i)$, 5.3 (a) $i)$ and 5.4 (a) $i)$. Taking the case of evolving *avoidance* as an example and again starting at initial values of low resistance optimal virulence should correspond to intermediate values of virulence. Since prevalence will be non-zero the host will be selected for some resistance. As host resistance increases there will be selection for increased virulence (since equilibrium susceptible density is increased by an increase in innate resistance). As parasite virulence increases the host is selected to higher values

of resistance (because the successful parasite invasions lead to higher prevalence). Therefore we expect a trajectory towards increased *avoidance* and increased virulence, however, due to the hump-backed relationship between *avoidance* and prevalence this increased resistance is likely to lead to intermediate prevalence. Therefore, here for *avoidance* as well as *clearance to immunity* the co-CSS can correspond to increased resistance and virulence relative to the purely evolutionary case. However with *avoidance* prevalence can not go beyond the intermediate level at which resistance is maximal whereas in *clearance to immunity* it is possible for coevolution to carry the disease to levels of high prevalence (the result here for *avoidance* is also true for clearance *without* acquired immunity, i.e it is generally true for innate resistance). Finally, the evolution of acquired immunity (through either the probability of acquiring immunity or the duration of acquired immunity) has no effect on susceptible density and hence as the host population evolves towards optimal values of acquired immunity there is no change in optimal virulence.

Coevolutionary models of host and parasite produce a range of evolutionary behavior but one of the most interesting results has concerned the co-CSS. Best et al [102] comment that evolution in the host can induce selection for highly virulent parasites that have much higher transmission and shorter infectious periods than predicted by purely evolutionary models because evolution to high resistance selects for high virulence and vice versa. They point out that such "fast", acute, and deadly parasites in natural settings are a cause for great concern. Our results here support these findings but they also extend them by evaluating them in comparison with the other modes of resistance. The epidemiological feedbacks depend on the mode of resistance and therefore the co-CSS effect depends on the mode of resistance. This demonstrates that the result reported in Best et al [102] is one of a number of interesting outcomes depending on which resistance is evolving. In particular, *avoidance* and virulence can co-evolve to high levels but importantly this is expected to correspond to intermediate levels of prevalence. An outcome that may be even more severe arises when *clearance to an immune state* (rather than *avoidance*) co-evolves with virulence for this time the ultimately high levels of virulence and resistance can correspond to high levels of prevalence. This could represent a more serious case since the parasite which has evolved to become deadly would be widespread in the population. Our results also highlight that evolving acquired immunity does not impact on selection for virulence which is clearly a more desirable situation from the perspective of intervention strategies. Therefore these results may be of interest to researchers in disease management since it suggests that in the long run some forms of resistance may be associated with deadly, widespread parasites, others with deadly parasites that are less widespread and still others with parasites that are relatively benign.

7.2 Conclusions

In this body of work we have modelled the evolution of virulence, both density dependent and density independent, as well as seasonal and non-seasonal. We have modelled the evolution of each of the fundamental forms of host resistance. Furthermore, we have modelled the evolution of resistance to a focal parasite when co-circulating parasites circulate in the host population. Therefore we have explored a range of important interactions outside the traditional scope of models of disease evolution. We have extensively interpreted these results and reported key insights into the behavior of these systems. Finally we have considered the implication of these results to more complex systems such as when hosts and parasites co-evolve. Future extensions to this body of work could include a more complete analysis of the coevolutionary relationships that have been sketched out in this discussion. In particular this will involve extensive simulations of the coevolution of host and parasite and the simulation results can be analysed with the insights here in mind. Furthermore, the assumptions of our modelling framework as discussed in depth earlier in this thesis can be relaxed and the results can be interpreted in comparison with this body of work. For example, the assumption that evolutionary and ecological timescales are separate can be relaxed (i.e. the assumption of weak selection through rare mutations of small effect). The recent theoretical approaches suggested by Sasaki and Dieckmann [196] as well as Day and Proulx [42] and Day and Gandon [43] may provide the analytical framework in which to test the effect of changes in these assumptions. Furthermore, fully stochastic simulations with a degree of genetic detail have the potential to demonstrate the relative strengths of evolutionary forces, in particular the strength of random drift and mutation compared to natural selection. The main difficulty is the mapping from genotype to phenotype which is poorly understood, however, models such as Boots et al [197] which show that it is possible to approximate genetic detail in phenotypic models point to ways in which these assumptions can be tested.

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